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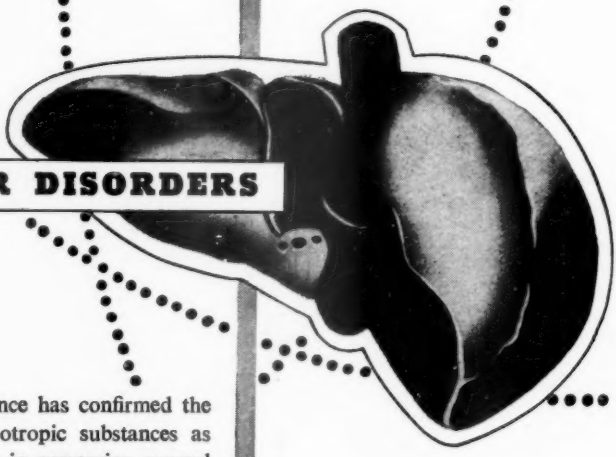

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**Vol. 46 No. 10 October 1953**

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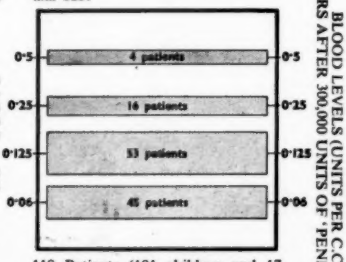


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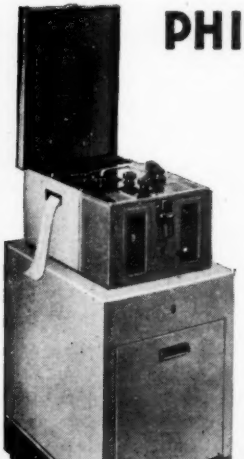

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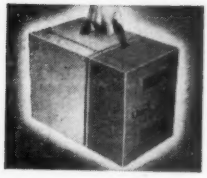

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# Section of Experimental Medicine and Therapeutics

President—Professor R. V. CHRISTIE, M.Sc.McGill, D.Sc.Lond., M.D., F.R.C.P.

[*May* 12, 1953]

## DISCUSSION ON POISONING WITH ANTICHOLINESTERASES

**Mr. R. Holmes:**

*The Physiological Mechanisms Involved in Poisoning with Anticholinesterases*

The effects of organo-phosphorus anticholinesterase drugs on mammals can be roughly divided into two groups, those resulting from the potentiation of peripheral cholinergic mechanisms, and those due to the action of the drug on the central nervous system. I shall discuss these two groups separately and then co-ordinate them in considering the cause of death from acute poisoning in experimental animals. The anticholinesterases used are the well-known TEPP, DFP and E600 (paraoxon), and Sarin and Tabun, which have been described by Holmstedt (1951).

Most of the peripheral effects of these drugs are due to the potentiation of post-ganglionic parasympathetic activity as a result of the nondestruction of acetylcholine at the effector cells. Thus miosis, salivation, rhinorrhœa and lacrimation result from anticholinesterase poisoning. Bronchoconstriction occurs, as a result of potentiated vagal activity, and is accompanied by increased secretion in the trachea and bronchi. Some bronchoconstriction also occurs in the poisoned vagotomized animal. The heart is slowed as a result of the continued presence of acetylcholine at the vagal endings, the effect being very much reduced if both vagi are cut before poisoning, thus removing the normal tonic discharge. Peristalsis is markedly increased with spasm of the small intestine, and defæcation and micturition often occur. Sweating results in these animals with cholinergic sweat glands. One of the most important peripheral actions of the anticholinesterases is the occurrence of neuromuscular block of the Wedensky type (Wedensky, 1885), that is, the inability of the muscle to maintain a tetanus from indirect stimulation although the response to single shock stimulation of the nerve or direct tetanic stimulation of the muscle remains. Douglas and Matthews (1952) have studied in detail the neuromuscular block of the diaphragm resulting from TEPP poisoning in cats.

Turning to the central nervous effects of these anticholinesterases one of the most striking effects of poisoning is the violent convulsions which occur. Wescoe, Green, Macnamara, and Krop (1948) have shown that DFP produces convulsive EEG patterns (increased discharge frequency at low voltage) in curarized cats and monkeys. Chennels, Floyd and Wright (1949) have investigated myographically the action of TEPP on spinal cord reflexes. They found that TEPP facilitates various reflexes (knee-jerk, flexor, and crossed extensor) and induces convulsions. The effects were due to a direct action of the drug on the central nervous system. I have found that in cats, intravenous injection of Sarin 200 μg./kg. abolishes the monosynaptic spike of the ventral root response to maximal stimulation of the dorsal root within about 20 seconds. This is followed by the inhibition of the polysynaptic spikes. Holmstedt and Skoglund (Skoglund, 1953) have obtained the same result with intra-arterial injection of 5 to 10 μg. of Tabun. They found, however, that DFP increases both the monosynaptic and polysynaptic reflex spikes.

The central action of the anticholinesterases which is of most significance in acute poisoning is the effect on the respiratory centre. Records of the nerve impulses in the upper root of the right phrenic nerve of a rabbit show that after 40 μg./kg. of Sarin intravenously, there is a gradual reduction in the impulse traffic which ceases completely 30 or 40 seconds from the injection. The interpretation of this action on the respiratory centre is not at all clear and, as with other central effects, depends on one's view of the role of acetylcholine in the central nervous system. The possibility that the effect is due to some reflex or reflexes from the periphery is ruled out since respiratory inhibition is obtained by intra-cisternal or intra-vertebral artery injection of the anticholinesterase (Wilson 1952, personal communication). It was thought that the inhibition of respiration might be due to repetitive discharge of the central vagal cells assuming these to be cholinergic, but no increase in discharge was found in the vagus nerve at the time of failure of the phrenic discharge. There were, however, massive discharges down the vagus after inspiration had stopped, and in the monkey these coincided with forced expirations. The timing of these discharges suggests that increased activity of the expiratory centre is the result, not the cause, of inhibition of the inspiratory centre.

The actions of the organo-phosphorus anticholinesterases which have been described can be observed in experimental work in general, but there are very large species differences in the severity of the various effects. Turning to acute anticholinesterase poisoning in the anæsthetized rabbit, cat and monkey, the inhibition of respiration is, in all cases, the cause of death. The circulation is impaired, but death is never due primarily to circulatory failure.

There are three important ways in which the anticholinesterases can affect respiration: by causing neuromuscular block of the respiratory muscles, bronchoconstriction and a direct inhibition of the central respiratory mechanism. In the rabbit, the bronchoconstriction is not usually severe; it does not reach its maximum until two minutes after the intravenous injection of 40 μg./kg. Sarin and then the tidal air was only 40% of normal (de Candole, Douglas and Spencer 1950, personal communication). A record of the diaphragm contractions in response to repetitive tetanic stimulation of the phrenic nerve shows that neuromuscular block occurs rapidly after anticholinesterase poisoning and this, in the past, led to the conclusion that death was due to asphyxia resulting from paralysis of the respiratory muscles. However, if the uncut phrenic nerve is placed on electrodes and the nerve is stimulated immediately after the spontaneous diaphragm contractions have stopped as a result of the injection of 40 μg./kg. Sarin, the diaphragm still responds with a tetanus. Records of phrenic nerve impulses show that the failure of the spontaneous diaphragm contractions is due to a gradual reduction and finally a cessation of phrenic impulses. The dose given is important here, since with a slightly smaller dose of Sarin, 30 μg./kg., the central inhibition is not quite so rapid, and developing neuromuscular block causes a transient stimulation of the respiratory centre before it is completely inhibited (Daly and Wright 1953, personal communication). With E600 1·5 mg./kg. and TEPP 250 μg./kg., the rate of inhibition of the respiratory centre is somewhat slower than with Sarin, thus after the intravenous injection of 250 μg./kg. TEPP to a rabbit, the diaphragm action potentials ceased in 20 seconds and the phrenic discharges stopped 37 seconds later.

The cat differs markedly from the rabbit in that bronchoconstriction is severe in anticholinesterase poisoning. With large doses, the bronchoconstriction can be sufficient to stop air intake completely although powerful inspiratory efforts continue. The respiratory efforts then suddenly cease, although in some cases, with the lower doses, air intake was quite good. It might be thought that this cessation of effort is due to asphyxia since cardiac output is reduced and the blood pressure lowered, but in the majority of cases at least, the rapid failure of inspiratory effort suggests that the inhibition of the respiratory centre is again the final cause of respiratory failure. Douglas and Matthews (1952) state that in the cat poisoned with TEPP, neuromuscular block is the most important cause of death besides the central inhibition; they studied the neuromuscular block at the diaphragm in considerable detail. In my experience, neuromuscular block at the diaphragm is not an important factor in poisoning with any of the anticholinesterases, DFP, E600, Sarin, Tabun or TEPP. This was shown by experiments in which both phrenic nerves were cut at least five minutes before the injection of TEPP 300 μg./kg., so that the diaphragm was completely flaccid. Air intake was apparently quite satisfactory with the chest muscles alone, and after the injection the inspiratory efforts continued showing marked bronchoconstriction as in the intact animal. Even though the chest muscles were more active than normally, there was clearly no significant amount of neuromuscular block since large intrapleural pressure differences were developed.

The monkey differs from both the rabbit and the cat in that neither neuromuscular block nor bronchoconstriction seems to occur to any significant extent in lethal anticholinesterase poisoning. The failure of respiration is due entirely to the central action of the drug. The course of respiratory failure has already been referred to and the effects of a just sublethal injection of Sarin (20 μg/kg. i.v.) are as follows: the inspirations are gradually reduced and cease altogether, to be followed by a period of forced expirations. These again cease and the succeeding apnœa is eventually broken by deep gasps which pass off into normal respiration. With a larger dose, the period of apnœa continued and the heart ceased. That the failure of inspiration after Sarin 30 μg./kg. is due entirely to a central action of the anticholinesterase has been shown graphically by plotting against time the number of impulses per inspiration in a single fibre of the upper root of the phrenic nerve of a monkey and the tidal air measured from the kymograph record. The two curves are very closely parallel.

Acknowledgment is made to the Chief Scientist, Ministry of Supply, for permission to publish these results.

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**Mr. W. K. Berry:**

*Biochemical Mechanisms Involved in Poisoning by Anticholinesterases*

The toxic phosphorus compounds dealt with are, di*iso*propyl phosphorofluoridate, DFP; ethyl NN'dimethyl phosphoramido cyanidate, Tabun; *iso*propyl methyl phosphonofluoridate, Sarin; and 3,3 dimethyl butyl-2 methyl phosphonofluoridate, Soman.

Of several enzymes tested *in vitro*, esterases, especially cholinesterase (ChE), are the most sensitive to these poisons. Both true and pseudo ChE are about equally affected by Tabun and Sarin, whereas true ChE is comparatively insensitive to DFP. True ChE is highly correlated with the function of the nervous system, and is found also in erythrocytes. Pseudo ChE, found in human serum, has no known physiological function.

All workers except Nachmansohn *et al.* (1947) are agreed that the inhibition of ChE by these poisons cannot be reversed by any known means. Nachmansohn claimed to have demonstrated a parallelism between nerve conduction and ChE activity. Both were inhibited by DFP, both could be restored by washing. The longer the exposure to DFP before washing the less the restoration, until finally there was no restoration at all. Aldridge (1950) demonstrated that Nachmansohn's experiments were wrongly interpreted, and that the reversal of inhibition of ChE was not measurable. The implication seems to be that DFP has actions not connected with inhibition of ChE.

*In vivo* studies by various people, e.g. Grob *et al.* (1947), show that a large number of blood and urine constituents are not affected by DFP. However, Davies and Douglas (1949) showed that during convulsions induced by Sarin, the blood sugar of goats rose sharply, probably secondary to the accompanying anoxia.

No enzymes other than ChE have been studied *in vivo*. A mass of conflicting data on the value of blood ChE's in assessing toxicity may be summarized by saying that the plasma ChE is useless, the erythrocyte ChE is of questionable value in assessing toxicity, although it may be useful as an index that poison has been encountered, and as a guide to the progress of recovery. The best index of toxicity appears to be brain ChE, which is, of course, not available for a large number of experiments.

Relationship between erythrocyte ChE and symptomatology depends to a large extent on the route and rate of administration. Unprotected men exposed to the vapour of DFP or Sarin, we find, can suffer extreme harassment without perceptible change in ChE. Masked men exposed to skin contamination can lose up to 85% of ChE before beginning to exhibit symptoms. Comparatively large oral or intravenous doses produce symptoms with little inhibition of ChE, whereas repeated small doses can produce a considerable fall in ChE without symptoms. Nevertheless, under such conditions animals appear to be unusually sensitive, since Muir and Callaway (1952) have found a significant lowering of the $LD_{50}$ of Sarin.

Recovery of blood and tissue ChE's is slow, and in the blood seems to be due to synthesis of fresh enzyme. The start of recovery of erythrocyte ChE is delayed for a day or two, in contrast to other tissues studied.

*Therapy.*—There have been two general lines of study, neutralizing the effect of accumulated acetylcholine, and the prevention of ChE inhibition. It is well known that atropine can often promptly reverse muscarinic symptoms. This is probably not due to reversal of inhibition of ChE, especially since atropine in therapeutic doses is completely without effect on ChE. This action of atropine suggests that these poisons have actions not connected with inhibition of ChE. The prevention of ChE inhibition appears to be the mechanism involved in Koster's (1946) finding that prophylaxis with eserine raised the $LD_{50}$ of DFP. However, this measure was completely useless as therapy, because eserine after DFP had a cumulative effect. Mr. A. Todrick and I thought that we might be able to find some simple chemical, resembling the active centre of ChE, which would be non-toxic, and yet able to combine with Sarin fast enough to protect against that inhibitor. We found, briefly, that 3,4 dihydroxyphenylalanine (DOPA) and other *o*-dihydroxybenzene derivatives were able to protect both true and pseudo ChE's against, not only Sarin, but also against Tabun and Soman, and, to a lesser extent, DFP. A direct DOPA-Sarin reaction seemed to be involved, but we had tentative reasons for supposing that the active centre of ChE was not phenolic. DOPA could not reverse inhibition by Sarin. The protective effect disappeared on dilution to a degree which was still therapeutically impracticable, so we thought that DOPA might be the precursor of a more active substance. A study of the products of enzymic and non-enzymic oxidation of DOPA failed to reveal any such.

I am indebted to the Chief Scientist, Ministry of Supply, for permission to communicate this paper.

Some of the experiments on DOPA involved the collaboration of K. P. Fellowes, B.Sc., P. J. Fraser, B.Sc., Ph.D., and J. P. Rutland.

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**Mr. D. R. Davies, and Mr. L. Austin:**

*The Chronic Effects of Anticholinesterase Poisoning*

Bidstrup and Hunter (1952) reported 2 cases of poisoning with NN′ di*iso*propyl phosphorodiamidic fluoride (Mipafox) which exhibited an unexpected symptomatic picture. 3 people developed acute poisoning while engaged on a pilot plant manufacture of this substance. Recovery from acute phase of the illness followed the administration of atropine in large doses but in the three weeks after the onset of symptoms, 2 of the patients developed paralysis of the limbs similar to that which follows tri*ortho*cresol phosphate poisoning. Petry (1951) has described similar effects after poisoning with parathion. Paralysis in man following intoxication with TOCP has been described frequently. Thus Lorot (1899) reported a number of cases of motor neuritis in tuberculous patients after treatment with "phosphocreosote". During prohibition in the United States TOCP was used as an adulterant of Jamaica Ginger, a non-alcoholic drink which was popular during this period. As a result, several hundred cases of paralysis occurred (Smith, Elvove and Frazier, 1930). Ter Braak (1931) and Sampson (1938) reported several other cases from the continent of Europe.

At the present time TOCP is used as a "plasticizer" and in 1944 Hunter, Perry and Evans described cases in this industry.

The appearance of these effects as sequelæ of poisoning with the new organo-phosphorus insecticides has resulted in a series of researches which have been designed to determine mechanisms by which paralysis is caused by these substances.

Three substances TOCP, DFP (di*iso*propyl phosphorofluoridate) and Mipafox will produce paralysis in chickens (Barnes and Denz, 1953; Earl and Thompson, 1952; David, 1951). Koelle, Gilman and Binzer (1946) administered DFP over a long period to cats and dogs with similar results. Previously Bloch (1941) and Hottinger and Bloch (1943) attempted to explain these effects in terms of the anticholinesterase properties of TOCP. They suggested that the inhibition of cholinesterase resulted in the production of excessive concentrations of acetylcholine at the nerve endings and that paralysis resulted from prolonged contact of the nerve with these high concentrations of acetylcholine.

More recently the effects of TOCP upon a number of widely different enzyme systems have been studied by Earl, Thompson and Webster (1953). They examined glucose and pyruvate oxidation by brain, trypsin, brain amine oxidase, pancreatic lecithinase and brain cephalinase. They found all these systems to be insensitive to this compound.

The tributyrinase activity of the spinal cord of hens poisoned with TOCP was found to be moderately reduced but in every experiment the pseudo-cholinesterase of the spinal cord has been inhibited to a greater degree.

Both DFP and Mipafox in company with TOCP are selective inhibitors of the pseudo-esterase. Thus all the available evidence suggested that demyelination might well be a consequence of anti-pseudo-cholinesterase action. Earl and Thompson (1952), in discussing these results, tentatively put forward the thesis that demyelination may result from the inhibition and continued depression of the pseudo-esterase of the spinal cord. Inasmuch as these authors had at that time worked only with TOCP it was desirable to examine this hypothesis further. We have therefore examined the possible demyelinating effects of the four powerful anticholinesterases mentioned in the previous paper, viz. DFP, Tabun, Sarin and Soman.

We set out to answer two questions: (1) Would all of these four substances produce demyelination in chickens and (2) could the cholinesterase changes be related to the ability of these to produce paralysis.

Chickens were injected subcutaneously with large doses of these substances. Since the doses were within the lethal range it was necessary to protect the birds with atropine.

The DFP-treated birds all developed chronic symptoms in ten to sixteen days. The course of development of symptoms was identical in every case. Immediately after dosing each bird exhibited the now familiar and typical symptoms of acute acetylcholine poisoning. These

lasted for twenty-four to forty-eight hours. There was then a symptom-free period of about ten days. They then showed signs of weakness. The subsequent clinical picture was identical with that described by Earl and Thompson following TOCP intoxication and by Barnes and Denz after Mipafox and DFP. They appeared quite normal in the cage, but when let out they walked unsteadily. On the following day they could be seen sitting on their heels in the cage; when released, they first behaved as on the previous day, but after a few minutes were unable to lift their heels from the ground. A few days later, the legs became completely useless and the birds sat with their legs outstretched unable to move. Apart from the paralysis the birds appeared to be completely healthy. After about a week of this state, however, they lost weight rapidly and a little later many of them showed cyanosis of the combs and gaping of the beak. At this stage many of them died, probably from inanition resulting from their inability to collect the food placed for them.

Histological examinations of the tissues showed demyelination of both the ascending and descending tracts of the central nervous system. *No* such changes, clinical or histological, were observed with Tabun, Sarin or Soman, despite heroic and prolonged dosing.

Thus in the case of Sarin doses were given twice weekly over a period of five weeks. Despite this long period of dosing, there was no clinical evidence of paralysis nor did histological examination produce evidence of nerve damage, although a number of these birds were under observation for as long as three months.

In order to compare the changes in the cholinesterases of the central nervous system, two groups, of about twenty-five birds each, were injected subcutaneously with DFP and Sarin. Since the doses used were within the lethal range each bird was protected with an appropriate dose of atropine sulphate. The birds were sacrificed in pairs from each group, at varying intervals over a period of three weeks. The first pair were killed two hours after injection. The brain and spinal cord were removed and homogenized. The enzyme assays were carried out in the Warburg and acetyl-$\beta$-methylcholine and butyryl choline were used to measure the true and pseudo-cholinesterases respectively.

(1) The true and pseudo-cholinesterases of the brain were inhibited equally by both DFP and Sarin. The rate of recovery of both enzymes was the same in each group.

(2) In the spinal cord DFP produced a slightly greater inhibition of the true enzyme than did Sarin. Otherwise there was no marked difference in the two groups. In the case of the pseudo-cholinesterase, however, Sarin produced only about 40–50% inhibition, whilst DFP caused almost complete inactivation of the enzyme. The rate of recovery after both inhibitors was very similar, but since it was inhibited to a much greater extent, the pseudo-esterase remained depressed at a significantly lower level and longer time after DFP. Since the hypothesis which these experiments was meant to test suggested that demyelination might result from the inhibition and *the continued depression of the pseudo-cholinesterase,* this difference with DFP as compared with Sarin was felt to be important.

A second experiment was therefore designed in which the method of administration of Sarin ensured that the same degree of inhibition resulted with Sarin and DFP. Furthermore, small additional doses of Sarin were given daily to ensure that the level of the spinal cord pseudo-cholinesterase was maintained at levels below that of the DFP groups. There were still no signs of paralysis or demyelination in the Sarin-treated group.

The conclusions that may be made from these investigations are quite clear cut.

*First:* We have been able to produce demyelination with only one out of four potent anti-cholinesterases which we have given to chickens, under comparable conditions.

*Second:* In a carefully designed experiment in which the cholinesterases change in the central nervous system of two groups of birds, one which received a demyelinating agent and the other a non-demyelinating agent, were compared, no differences were observed which could account for the pathological effects.

From this, we think that it is extremely unlikely that demyelination is the direct result of either true or pseudo-cholinesterase inhibition. These conclusions are in full agreement with the findings of Barnes and Denz (1953) and also those of Davison (1953). These workers studied six organo-phosphorus compounds. They showed that with three of them, DFP, Mipafox and TOCP, they could produce demyelination in chickens regularly and in rats, dogs and cats occasionally. They were not able to do so with any of the other three. Davison showed very clearly that there were no distinguishing cholinesterase changes in the two groups.

Thompson in later experiments has also confirmed these conclusions, for he investigated a very highly selective inhibitor of pseudo-cholinesterase, NN′ *iso*propyl phosphorodiamidic anhydride or DPDA ("*iso* OMPA"), without producing paralysis or demyelination.

*Conclusion.*—Some organo-phosphorus compounds can produce demyelination, others do not. Species, notably the chicken, and to a lesser extent the rat and dog, are more susceptible to the chronic action of these substances than others. The site of the lesion which is essentially a motor neurone lesion is, in general, to be found in the ascending and descending tracts. Its position, however, varies with the species.

Because we have no real clue as to the precise mechanism by which these substances cause paralysis it is impossible to prophesy whether a given substance will, in fact, act in this manner. The extensive use of organo-phosphorus compounds in agriculture and the continued development of new agents to this end emphasize the need for research upon the mode of action of these organo-phosphorus demyelinating agents.

*Acknowledgments.*—We wish to thank the Chief Scientist, the Ministry of Supply, for permission to publish this paper. One of us (L.A.) is on detached duty from Dept. of Supply, Australia. Consequently, we also wish to thank the Senior Representative, Dept. of Supply, Australia.

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# Section of Orthopædics

President—H. JACKSON BURROWS, M.A., M.D., F.R.C.S., F.R.A.C.S.

[*March* 3, 1953]

## An Even Keel in Orthopædics [*Abridged*]

### PRESIDENT'S ADDRESS

By H. JACKSON BURROWS, M.A., M.D., F.R.C.S., F.R.A.C.S.

IN their Presidential Addresses, some have described their original work. Others have used the occasion to air their views in general without fear of debate or contradiction. This is what I propose. Many of the things I have to say, you will, I hope, be thinking already; if so, you can call them platitudes, but nevertheless I believe they need saying. With other observations you will severely disagree; these, even more, I deem worth saying. If I appear captious, I plead that the temple of science is entered through the portal of doubt.

We all of us often buttonhole a colleague, stick up a film and say "What would you do with this?" That laudable exercise sometimes prompts us to "do something, even if it's wrong", a reminder of the unkindly definition of a younger branch as "the pursuit of the inoperable by the irrepressible". As a new clinical student I was surprised and shocked when a professor of medicine, now Sir Francis Fraser, stated that most patients come in search, not of treatment, but of peace of mind. Many postpone visiting a surgeon because they believe that to do so is to court operation—and how right they often are! In some ways those patients involve more responsibility than any, because they are an easy prey to the unscrupulous. In particular there is the mother, fearful of some hidden defect in her child that, neglected now, may blight his future. Apprehensiveness has brought a big demand for treatment, especially among the better-to-do, who, being perhaps more provident, are often more solicitous. How ready the profession has been to meet this demand! More than half the boys leaving public schools have lost their tonsils, and as many as four in five their foreskins. One wonders how many have been subjected to wedged shoes and so-called remedial exercises: certainly a very large number, and I am persuaded that it is scarcely possible to be a really nice young man without having endured these indignities of initiation.

A child who intoes because of tibial torsion counteracts this by flattening his feet. If valgus wedges are prescribed he will intoe even more and will probably be taken elsewhere. None can cavil at correction of valgus feet in a child with knock-knees, but any wedge is too great that throws the foot into varus; nothing encourages knock-knee so much as pes varus. Normal children go through a phase of knock-knee, which soon disappears if they are lucky enough to avoid treatment; if, on the other hand, they have to contend with a man-made pes varus, they usually still get well, but much more slowly. I am not speaking of that textbook extravagance, the quarter-inch wedge; it is impossible; its victims never return, and so it continues to be sponsored.

"Remedial exercises" are a worse expedient than wedges, because more time-consuming, more expensive and more harmful. In one girls' school, five in every seven pupils perform daily the rite of "flatters", described in the school bill as remedial exercises. Granted mobility, postural re-education must aim at a plantigrade foot with correction of the everted heel. In traditional remedial exercises a plantigrade foot is avoided at all costs, and the ball of the great toe never touches the ground except in tip-toeing. When I was a child our nannies (beloved but now extinct race) made us turn our toes out; nowadays our physiotherapists would make us walk on the outer sides of our feet: better nanny's valgus than physio's varus. Another very bad custom among many physiotherapists is the passive stretching of tight posterior calf muscles, which must respond by becoming tighter still; physiological relaxation is promoted by active dorsiflexion without pronation. Taking my cue from A. P. H. I hope to launch the S.L.P.L.B.A.[1] Advice to do nothing demands far more careful explanation than advice to do something, and due warning against the well-meant promptings of friends.

Hilton wrote "Pain the monitor, and rest the cure, are starting-points for contemplation that should ever be present to the mind of the surgeon in reference to his treatment." We all like to base conservative treatment on so-called "principles", like "rest" and "movement", but we should bear in mind—as clearly Hilton did—that these are abstractions. Complete rest is incompatible with life. R.I.P. spells "enforced, uninterrupted, and prolonged rest."

Misuse of rest now provides a less abundant harvest for the bonesetter than it did. But it is still one cause of porotic bones, damaged growth plates, and stiff joints. Splinting paralysed parts did

[1] Society for Leaving the Poor Little Blighters Alone.

not stiffen joints when these were put daily through their full range of movement subject to the dictates of pain. It was the misuse of splints, and an exaggerated campaign against passive movements in all circumstances, that produced the stiffened joints in paralysed limbs. Against these bad results of bad treatment there arose a worse reaction. Painful limbs in the active stage of poliomyelitis were moved, not with restraint, but forcibly and mercilessly with a violence that tortured patients, promoted spasm in still active muscle and even caused myositis ossificans—often the badges of ill-treatment, of a paretic limb no less than of an injured elbow in a child.

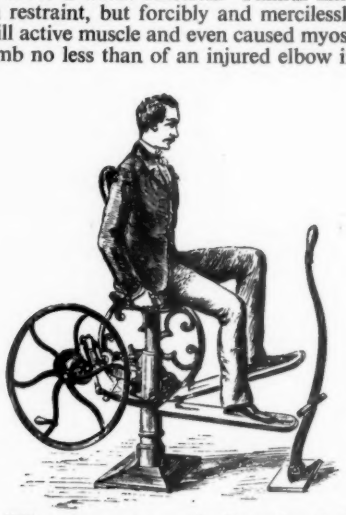

FIG. 1.—The velocipede. "The movements must be discontinued when slight fatigue is felt."

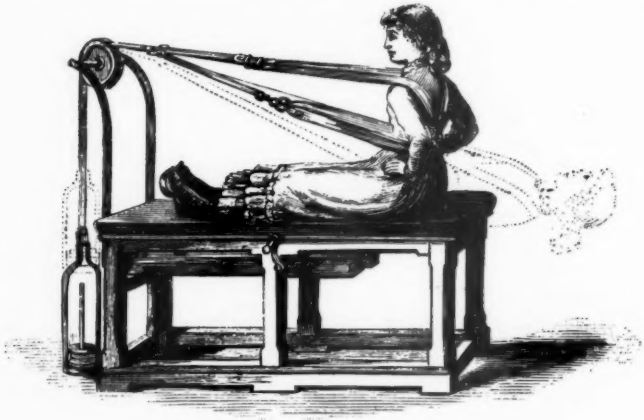

FIG. 2.—Active exercise against resistance in 1883.

The strengthening effect of muscle re-education has obscured its other principal effect—the physiological promotion of relaxation in unparalysed opponents. This can be encouraged before any power has returned to the paralysed muscles if the patient makes early attempts to contract them.

Active exercise, the basis of physiotherapy, must be tempered with wisdom. Although the remedial gymnast and the carpenter, under proper supervision, might be employed more often, the enthusiastic misuse of pulley exercises, occupational therapy, rehabilitation centres and convalescent depots has, by and large, delayed recovery as much as their intelligent use has promoted it. Our grandfathers used apparatus often differing little from our own (Figs. 1–4), but ordained that "The movements must be discontinued when slight fatigue is felt."

Before leaving the subject of conservatism I would like to say a few words about appliances for paralysed children. In spastic paralysis, splinting is as commonly neglected as operation is abused. In flaccid paralysis, it has become customary to condemn appliances for children. Yet many adults show irremediable stretching of the ligaments of the knee, for instance, which would have been

prevented by the intelligent use of a caliper in childhood. To unfetter the boy is sometimes to fetter the man. Surely this is a matter in which the most careful and unemotional judgment of each patient must be combined with the utmost vigilance.

It might be debated that a man can be a quite good orthopædic surgeon without operating at all. *Chirurgery* is work with the hands, and many of us are not nearly expert enough in conservative orthopædics. Percivall Pott, writing in 1760, said that "there are many disorders strictly within the surgeon's province, the management of which will require more real skill, and judgment, than are necessary for the mere performance of any operation whatever; not to add, that the power and capacity of a practitioner are full as often shown by preventing an operation, as in performing it." A surgeon who subjects his patient to treatment that he would not allow in his own kin betrays his patient. In an age when cleverness is often prized above wisdom and integrity, the paramount importance of the patient's interests cannot be stressed too strongly. Some surgeons have found in the intervertebral disc not a jelly-like nucleus pulposus but a glittering nugget of gold: a great surgical advance has been discredited by misuse.

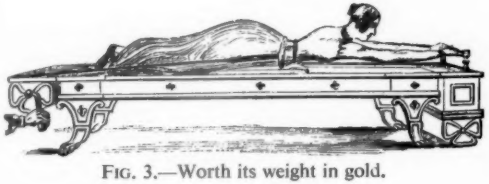

FIG. 3.—Worth its weight in gold.

FIG. 4.—Hospital model.

Figs. 1, 2, 3 and 4 are reproduced from *The Journal of Bone and Joint Surgery*, **35**-B, 321–323, by kind permission of the Editor.

The development of arthroplasty of the hip is another great advance of our time, and a lasting memorial to Smith-Petersen, but it remains a truism that a surgeon may make provision for his later years by "doing some cups" in his youth. A stern task confronts those who will have to deal with the failures of the Judet operation, so recent an experiment as to be rarely proper in any but the aged.

In congenital dislocation of the hip, the old description of closed reduction as "bloodless" was misleading, if not dishonest. Nevertheless it seems possible that the present reversion to operative reduction has been overdone, that the ovaries are too readily endangered in radioscopic arthrography, and that the need for rotation osteotomy is recognized too seldom and too late.

There are still devotees of prolonged pre-operative skin preparation, which makes every razor-scratch a menace. "No-touch-technique" remains part of the orthopædic gospel for most of us, and I suppose that even the unbelievers do their meniscectomies thus. Little harm comes of our pet foible unless it promotes neglect of bigger things. Things that really matter in meniscectomy are how you select your case, mask your face and drape the limb (the fashionable stockinette with Mastisol loosens desquamated epithelium and deposits it in the wound), whether you see inside the joint what you ought to see, and whether you can do an adequate operation without using dangerous or fancy instruments. There are occasions for the adage "Put your finger in it or you'll put your foot in it". A gloved finger is unlikely to harm a joint if talcum powder is avoided, but in bone operations the glove is likely to be punctured. A famous surgeon lays his instruments on a pretty blue and white towel identical with the International Code Flag A, which means "I am undergoing speed trials"; for lesser men there is the D flag, "I am manœuvring with difficulty."

In our youth most of us have designed gadgets, and in our maturity have regretted them. A gadget has had spectacular success in Key's compression arthrodesis of the knee, popularized by Charnley, but technical interest has obscured what I believe to be a most important fact, namely that, whatever the patient's occupation, a knee should never be fused nearly extended. A patient with a straight knee cannot sit back in a chair; he must sit on the edge to allow the heel to touch the ground, and

his foot sticks forwards as far as it will go. If the knee has 30 degrees of fixed flexion he can sit back in the chair with the foot supported on its fellow and projecting about half as far. In normal walking the weight-bearing knee is always flexed 16 degrees or more (Elmslie).

Few of us give enough forethought to our treatment, especially to the more mechanical operations. It is said that Nansen, on his return from the Antarctic, was asked whether many things happened that he hadn't foreseen. "No," he replied, "but many things I had foreseen didn't happen." Foresight and imagination are necessary, and also a physiological approach. In John Hilton's words, we must be "Nature's willing servants". The whole patient in his own surroundings is easily forgotten in making our plans. How often has the pursuit of "orthopædic principles" converted a person who could sit but not stand into one who could stand but not sit? The supreme example is provided by the orthopædic epitaph "He died in perfect position". I knew a natural exhibitionist with flail legs, who earned a reasonably happy competence by walking about race courses and football fields on his hands with his feet tucked into his waistcoat pockets. Someone fused one knee and the patient was ruined. Later the other knee was fused, equally unwisely, and ultimately his legs were cut off through the thighs. In poliomyelitis an ill-judged lengthening of the tendo achillis notoriously can impose a caliper for life, but in spastic paralysis it can cause the most devastating multiple deformities.

Bone operations on growing feet provide a more controversial subject. I believe them to be rarely excusable. When I was a registrar at the Royal National Orthopædic Hospital I saw a master perform many arthrodeses most beautifully on young children's feet. Later, I inherited these patients and have seen the often deplorable results, irredeemable by further surgery. Among the badly disabled children at the Heritage, Chailey, such feet present some of our worst problems—feet that have been ruined less by the hand of disease than by the hand of man.

The place of orthopædics in the medical curriculum has long been debated. Lambrinudi emphasized the unity of medicine, and showed that its principles could be better demonstrated in orthopædic patients than, perhaps, in any other. He believed that we should get clinical students early before they have jettisoned the relevant part of their preclinical training with the irrelevant. The demand by students for orthopædic teaching is almost insatiable. It offers unparalleled opportunities for: history taking; observation; the elicitation of physical signs; the interpretation of these in terms of mechanics, anatomy, physiology and pathology; the testing of the consequent provisional diagnosis by special methods of examination; the logical prescription of treatment with a regard for function and personality; the final summing-up with the pros and cons of the diagnosis and proposed treatment; and finally the lucid explanation to the patient—I specially mention this, because students, in my experience, get little help from their teachers in learning how to talk to patients and their relatives; few know instinctively; some never learn.

The undergraduate schools cannot for ever live in the past, and ignore or suppress the so-called special departments. A false conception of education imposes on the great undergraduate teaching hospitals the pattern of the cottage hospital, to the great detriment alike of their patients and of medical education.

It is often said, and is too rarely questioned, that undergraduate and postgraduate teaching cannot be conducted in the same school. In point of fact many undergraduate schools undertake some postgraduate *teaching*, and all do a great deal of postgraduate *training*. It may be questioned whether more than this is needed, but I hope that a place will be conceded for distinct postgraduate schools with facilities for special experience, for observing the work of many surgeons, and above all for orthopædic pathology and research.

One wonders whether the rather cut-and-dried path that has been laid out for the would-be consultant is too vocational, with too little provision for experience in research. In our emphasis upon a technological training, far beyond any we accomplished ourselves, are we discouraging that cultivation of individuality that is rightly called education. It would be sad to see the postgraduate schools crowded with candidates for a diploma. A university degree is a different matter, especially if awarded for original work; formal examinations might cease with the Fellowship.

Postgraduate study is naturally of special interest to me, and before leaving the subject I should like to pay tribute to the Liverpool school. It is our oldest; its fame is world-wide; it commands an *esprit de corps* that all can envy; and we of a much younger school at the Institute will ever remember the kindness, help and encouragement that we have always had from our older brother.

Finally let me defend this rambling discourse by quoting John Moyle, a Naval Surgeon of three centuries ago, and plead that "it is not founded upon frothy notions, but it is the product of real experiences".

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Correction.—*Proceedings*, Vol. **46**, p. 344, May 1953.

**The Use of Radioactive Phosphorus in Early Detection of Avascular Necrosis in the Femoral Head in Fractured Neck of Femur.**—G. P. ARDEN and N. VEALL.

Line 7.—"0·1 mm. of tissue absorbing 90%" *should read* "1·0 mm. of tissue absorbing 50%".

Line 12.—"approximately 200 mc. of $P^{32}$" *should read* "approximately 200 μc. of $P^{32}$.

# Section of Epidemiology and Preventive Medicine

President—Professor ROBERT CRUICKSHANK, M.D., F.R.C.P., D.P.H.

[*April* 17, 1953]

## The Control of Tuberculosis: Preventive Measures in Chest Clinics [*Abridged*]

By R. GRENVILLE-MATHERS, M.D., and H. J. TRENCHARD, M.R.C.P.

**Dr. R. Grenville-Mathers:** Apart from temporary setbacks during the two Great Wars, the deaths from tuberculosis have over the last one hundred years steadily declined due to improved social conditions, and the chest clinic service started in 1913 has had little influence on this decline until the last few years when streptomycin has been available. Yet the complete surveys recently carried out in the Rhondda Fach (Cochrane *et al.*, 1952; Jarman, 1953) indicate that the percentage of tuberculin-positive children there is similar to that found in the Country as a whole (Medical Research Council, 1952); and it is therefore quite likely that the high incidence of tuberculosis found in the Rhondda Fach is applicable elsewhere. The amount of tuberculosis in the population is much greater than has often been thought.

The chest clinic areas, Harrow and Edgware, from which the data here reported are derived, are situated in the North-West Metropolitan Hospital Region, which has comparatively few beds for the treatment of tuberculosis (Table I), and in spite of the clinic nomination scheme

TABLE I.—POPULATION PER BED FOR TREATMENT OF TUBERCULOSIS IN VARIOUS HOSPITAL REGIONS

| | | | |
|---|---|---|---|
| Wales ... ... ... ... | 1,030 | E. Anglian ... ... ... | 1,610 |
| Liverpool ... ... ... ... | 1,090 | Birmingham ... ... ... | 1,640 |
| Newcastle ... ... ... ... | 1,260 | N.W. Metropolitan ... ... | 1,750* |
| S. Western ... ... ... ... | 1,370 | Sheffield ... ... ... ... | 1,800 |
| N.E. Metropolitan ... ... ... | 1,500 | Manchester ... ... ... | 2,080 |
| S.W. Metropolitan ... ... | 1,520 | Oxford ... ... ... ... | 2,160 |
| S.E. Metropolitan ... ... ... | 1,590 | B.M.A. recommends ... ... | 1,000 |

TABLE II.—PERIOD OF FOLLOW-UP OF TUBERCULIN-POSITIVE CHILDREN

| Time of observation (years) ... ... | ½ | 1 | 2 | 3 | 4 | 5 | More than 5 |
|---|---|---|---|---|---|---|---|
| Index case sputum positive ... ... | 16 | 25 | 30 | 17 | 6 | 5 | 2 |
| Index case sputum converted ... ... | 9 | 28 | 13 | 7 | 4 | 1 | 5 |
| Index case sputum negative ... ... | 6 | 5 | 9 | 2 | 4 | 2 | 3 |
| Total | 31 | 58 | 52 | 26 | 14 | 8 | 10 |

for arranging admissions it has been necessary to practise domiciliary treatment extensively (Trenchard, 1949, 1951). We have been very concerned to surround each patient by a "zone of hygiene" to avoid further infection, and the preventive measures used have comprised (1) rehousing, for which specific recommendation is made to the M.O.H. and (2) education of the patient which starts immediately on diagnosis at the clinic. The tuberculosis health visitors give instructions concerning coughing, disposal of sputum, use of paper handkerchiefs or disinfection of handkerchiefs before washing, the necessity for separate crockery, cutlery and towels and their washing, and the need for a separate bedroom or at least a separate bed.

An average of 4 domiciliary contacts have been examined for each tuberculous case diagnosed, and all children have been tuberculin tested, usually by the jelly patch test which we regard as being equivalent to 0·1 mg. Old Tuberculin (Anderson *et al.*, 1951). On first examination of 818

children, 36% were tuberculin-positive out of 518 in contact with a sputum-positive index case, and 11% out of 300 with a negative index case. Amongst the positive reactors 23 children had a definite tuberculous lesion when first examined, so the damage done by the index case before diagnosis was quite considerable. Of the 222 initially tuberculin-positive children followed for 510 child years, average 2·3 years (Table II), only 2 subsequently developed lesions—1 meningitis after a year and 1 pleural effusion after six months.

Of 595 initially tuberculin-negative children followed for 1,213 child years, average more than two years, 101 conversions occurred. As the group is unselected it includes children with careless as well as careful index cases. We believe that the reason for so many remaining negative is the hygiene observed by the patients under the direction of the health visitors. The period of follow-up of these children and their tuberculin conversion rates are given in Tables III and IV. The national conversion rates reported by the Medical Research Council

TABLE III.—FOLLOW-UP OF TUBERCULIN-NEGATIVE CHILDREN SHOWING NUMBER CONVERTING

| Time of observation (years) | ½ | 1 | 2 | 3 | 4 | 5 | More than 5 |
|---|---|---|---|---|---|---|---|
| Index case sputum positive | 46 | 54 | 27 | 14 | 13 | 9 | 7 |
| Index case sputum converted | 16 | 52 | 39 | 22 | 12 | 9 | 9 |
| Index case sputum negative | 54 | 85 | 64 | 37 | 14 | 9 | 3 |
| Total | 116 | 191 | 130 | 73 | 39 | 27 | 19 |
| Number tuberculin converted | 35 | 25 | 15 | 6 | 9 | 10 | 1 |

TABLE IV.—TUBERCULIN CONVERSIONS (PERCENTAGE RATES PER ANNUM)

| Time (years) | ½ | 1 | 2 | 3 |
|---|---|---|---|---|
| All tuberculin-negative children | 11·6 | 10·4 | 5·2 | 3·7 |
| Those in contact with persistently sputum-positive index cases | 24 | 20 | 10 | 9·3 |

(1952) are 4·9 at ages 5 to 14 and 9·3 at ages 13 to 20. Of children in contact with sputum-negative cases 11% were discovered at initial contact examination to be tuberculin-positive, a proportion identical with that found on testing a group of non-contacts of similar age. Using this as a base line, a semi-logarithmic curve shows that even if the index case had been infectious for one or possibly two years before diagnosis the institution of general hygiene measures leads to a considerable diminution of infection.

Of the 101 children who underwent tuberculin conversion altogether 18 developed tuberculous lesions over a period of five years. The majority of these lesions were benign. They must be compared with 23 lesions discovered on first contact examination. The greater damage had been done while the index cases were unknown cases. An analysis of 136 consecutive notifications of tuberculosis in children in Harrow is shown in Table V, from which it can be seen that an

TABLE V.—SOURCES OF INFECTION OF 136 CONSECUTIVE CHILD NOTIFICATIONS (PERCENTAGES)

| | | | |
|---|---|---|---|
| No source discovered | 67 | Disease developed after known contact broken | 7 |
| Source found on contact examination | 8 | | |
| Child diagnosed as result of initial contact examination | 12 | Total infection from known source | 13 |
| Disease developed while in contact with known case | 6 | Total infection from unknown source | 87 |

unknown source is usually responsible for infection and the preventive value and importance of finding the unknown cases in our midst can be appreciated. The age distribution of new tuberculous cases in Harrow is shown in Table VI. There is a big jump in the number of cases in the age group 15–24 which corresponds with the jump in positive tuberculin reactors

TABLE VI.—HARROW URBAN DISTRICT, JANUARY 1949–JUNE 1950. NEW CASES OF TUBERCULOSIS PER 1,000 POPULATION. 295 MALES AND 220 FEMALES

| Age | Males | Females | Age | Males | Females |
|---|---|---|---|---|---|
| 0 – 4 | 1·5 | 1·3 | 35–44 | 8·9 | 1·3 |
| 5 – 14 | 1·5 | 1·5 | 45–54 | 10·3 | 0·4 |
| 15 – 19 | 9·4 | 4·5 | 55–64 | 7·3 | 0·3 |
| 20 – 24 | 7·1 | 6·4 | 65 and over | 3·7 | 0·6 |
| 25 – 34 | 4·1 | 3·6 | | | |

shown in Table VII. This high rate of infection and disease in those who have recently left school results from contact with unknown cases of phthisis at work and elsewhere. It suggests that an effective method of use of B.C.G. might be on school-leavers by the school medical service.

TABLE VII.—EDGWARE AND HARROW CHEST CLINICS. PER CENT POSITIVE TUBERCULIN REACTORS, 1951–52. 2,420 MALES, 2,819 FEMALES (MAINLY CONTACTS)

| Age | Males | Females | Age | Males | Females |
|---|---|---|---|---|---|
| 0 – 4 | 15 | 15 | 35–39 | 79 | 77 |
| 5 – 9 | 21 | 24 | 40–44 | 76 | 69 |
| 10 – 14 | 25 | 25 | 45–49 | 85 | 66 |
| 15 – 19 | 40 | 35 | 50–54 | 74 | 61 |
| 20 – 24 | 55 | 46 | 55–59 | 62 | 60 |
| 25 – 29 | 67 | 63 | 60 and over | 69 | 58 |
| 30 – 34 | 83 | 66 | | | |

**Dr. H. J. Trenchard:** The search for unknown cases of phthisis, the reservoirs of infection, requires radiography. Mass radiography in England and Wales up to 1948 found 3·9 cases per thousand out of nearly 3,000,000 examinations and (*see* Table VIII) a rather lower rate was

TABLE VIII.—PULMONARY TUBERCULOSIS CASE FINDING PER 1,000 EXAMINATIONS

| | Number examined | Rate per 1,000 |
|---|---|---|
| Mass radiography Harrow and Edgware 1948 ... ... ... ... ... ... | 11,089 | 2·8 |
| Routine Factory Radiography Harrow 1948–49 ... ... ... ... ... | 9,411 | 1·7 |
| Routine X-ray of Antenatal patients Harrow and Edgware 1952 ... ... | 873 | 1 |
| MacDougall *et al.* (1953) contacts of tuberculin-positive young school children ... ... ... ... ... ... | 3,789 | 4 |
| Doctors' referred cases Harrow Chest Clinic 1948–50 ... ... ... ... ... | 2,620 | 65 |
| Doctors' referred cases Edgware Chest Clinic 1949–50 ... ... ... ... ... | 5,753 | 32 |

found in the Edgware and Harrow chest clinic areas. Annual X-ray at a factory produced a still lower incidence presumably due to elimination of some cases by earlier examination, and routine radiography of antenatal women a rate smaller than has at times been reported. The excellent case-finding method at Bournemouth reported by MacDougall *et al.* (1953) found 4 tuberculous cases per 1,000 tuberculin jelly tests as a result of tracing domiciliary contacts of young school children with positive reactions. By providing facilities for general practitioners to refer patients they had selected for X-ray we have found a much higher incidence of tuberculosis. The difference between the rates at Harrow and Edgware in the years given in Table VIII was, as reported earlier (Trenchard and Grenville-Mathers, 1952), due to the cramped accommodation at Harrow. An X-ray could only be taken after making an appointment by telephone and the extra trouble involved doubtless made the practitioners very selective in referring cases. In 1951 Harrow Chest Clinic was moved to more commodious premises and X-rays could be arranged without making a special appointment, as had been the practice of the Edgware Chest Clinic. In consequence the numbers referred increased and the rate of case finding fell to figures comparable with Edgware. This is shown in Table IX which also indicates that there is a "law of diminishing returns" inherent in this method of case finding which is therefore not worth

TABLE IX.—PULMONARY TUBERCULOSIS CASE FINDING BY X-RAY OF DOCTORS' REFERRED CASES AT EDGWARE AND HARROW CHEST CLINICS 1948–52

| | Year | Annual examinations Males | P.T. per 1,000 Males | Annual examinations Females | P.T. per 1,000 Females |
|---|---|---|---|---|---|
| Edgware ... | 1948 | 906 | 40 | 1,105 | 21 |
| | 1949 | 1,175 | 47 | 1,435 | 29 |
| | 1950 | 1,445 | 33 | 1,698 | 21 |
| | 1951 | 1,633 | 29 | 1,922 | 16 |
| | 1952 | 1,560 | 29 | 1,797 | 16 |
| Harrow ... | 1948–50 | 395 | 92 | 478 | 35 |
| | 1951 | 1,284 | 45 | 1,529 | 24 |
| | 1952 | 1,657 | 32 | 1,946 | 22 |

extending indefinitely. We estimated that if the rate of case finding falls below about 20 per 1,000 examined the cost per case discovered tends to rise rapidly, and such work would be better undertaken by the mass radiography units. Approximately one-third of tuberculous cases are symptomless (Trenchard, 1945) and not therefore likely to see their doctors and be referred for X-ray. Mass radiography is, or could be, a preventive weapon of great value in the discovery of infectious foci in the apparently healthy part of the population, particularly if employed on the lines used in the Rhondda Fach scheme. Chest clinics in our view should concentrate on the examination of the apparently unwell, the contacts of tuberculous patients (as part of the practice of social medicine) and perhaps the examination of groups at special risk (antenatal patients and certain occupations).

In Table X is set out the age grouping of patients referred for X-ray by their doctors. It is to be noted that without special prompting the practitioners in the area send the right aged

TABLE X.—AGE DISTRIBUTION OF PATIENTS REFERRED FOR X-RAY BY THEIR DOCTORS 1948–52

| | | Males | | | Females | | |
|---|---|---|---|---|---|---|---|
| Age | | 15-39 | 40-64 | 65 and over | 15-39 | 40-64 | 65 and over |
| Edgware ... | 1948 | 578 | 305 | 23 | 795 | 287 | 23 |
| | 1949 | 695 | 419 | 61 | 989 | 413 | 33 |
| | 1950 | 843 | 551 | 51 | 1,194 | 475 | 29 |
| | 1951 | 903 | 629 | 101 | 1,276 | 583 | 63 |
| | 1952 | 743 | 712 | 105 | 1,156 | 568 | 73 |
| Harrow ... | 1948–50 | 689 | 453 | 42 | 977 | 411 | 48 |
| | 1951 | 642 | 575 | 67 | 948 | 520 | 61 |
| | 1952 | 770 | 769 | 118 | 1,222 | 661 | 63 |

patients for discovering pulmonary tuberculosis—young women and young and older men (*see* Table VI). It may be that the older men are referred in an effort to exclude bronchial carcinoma. From Tables XI and XII can be seen how important the X-ray of doctors' referred cases has become in our areas as a means of discovering previously unknown sources of infection.

TABLE XI.—EDGWARE CHEST CLINIC 1949–52. DOCTORS' REFERRED CASES AND CONTACTS

| | Total number examined | P.T. per 1,000 |
|---|---|---|
| Doctors' cases referred for X-ray ... ... ... | 12,665 | 27 |
| Contacts (new) ... ... ... ... ... ... | 6,045 | 15 |
| Contacts (Total new examinations plus re-examinations) ... ... ... ... ... ... ... | 16,589 | 6 |

TABLE XII.—SOURCE OF CASES TAKEN ON TO CHEST CLINIC'S REGISTER 1950–52

| | Referred by doctor for X-ray | Diagnosed elsewhere | Contact examination | Mass Rad. |
|---|---|---|---|---|
| Edgware ... ... ... | 251 | 196 | 59 | 40 |
| Harrow ... ... ... | 289 | 147 | 41 | 67 |

The findings of Mantoux testing school children in the area are given in Table XIII. The level of sensitivity is lower than that found in the M.R.C. national survey even allowing for the different strength of O.T. employed. At nine schools surveys were carried out because of a pupil or teacher being found to have tuberculosis. The results, some of which have been

TABLE XIII.—PERCENTAGE INCIDENCE OF POSITIVE REACTORS TO 0·1 MG. TUBERCULIN AMONGST 2,571 SCHOOL CHILDREN, WITH THE M.R.C. "SOUTHERN URBAN" (1 MG. O.T.) FINDINGS FOR COMPARISON

| Age ... ... ... | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 |
|---|---|---|---|---|---|---|---|---|
| Edgware and Harrow ... ... | 11 | 13·4 | 14·9 | 16·3 | 20·2 | 20·2 | 26·4 | 23·5 |
| M.R.C. (S. Urban) | 27·4 | 31·1 | 31·9 | 34·6 | 40·3 | | 51·0 | |

reported earlier (Anderson and Grenville-Mathers, 1952), are summarized in Table XIV. Only 3 previously unknown tuberculous cases were discovered. There seemed to be little evidence of much spread of infection from a tuberculous school child although an infectious school-teacher (schools numbered 8 and 9) may cause anxiety. There is a case for annual X-ray of school-teachers, but the introduction of a regulation on this subject would, in all fairness, need to be accompanied by a guarantee of full pay until well and able to resume work should a lesion be discovered.

There are potential dangers in rehousing a tuberculous family particularly if extra expense is entailed through a higher rent or a more costly journey to work leading to economy in money spent on food. Nevertheless, rehousing is at times required in order to obtain a satisfactory

TABLE XIV.—RESULTS OF TUBERCULIN (0·1 MG. O.T.) SURVEYS AT NINE SCHOOLS. AT THOSE MARKED * A COMPLETE SURVEY OF SCHOOL WAS CARRIED OUT WITHOUT FINDING FURTHER CASES

| School | Age of class | No. examined | No. tuberculin +ve | Expected No. positive: Local Survey | Expected No. positive: M.R.C. S. Urban Survey | Remarks |
|---|---|---|---|---|---|---|
| 1 | 6 | 41 | 1 | | 4 | Index case: child with primary lesion. Teachers' X-ray normal |
| 2 | 12 | 36 | 6 | 5 | 11 | Index case: child with pleural effusion. Teachers not X-rayed |
| 3 | 14 | 38 | 13 | 6 | 13 | Index case: child with +ve sputum. Teacher with inactive lesion. Two further primary lesions in children found |
| *4 | 14 | 36 | 5 | 6 | 10 | Index case: child with +ve sputum. Teachers' X-ray normal |
| *5 | 15 | 64 | 11 | 13 | 26 | Index case: child with primary lesion |
| 6 | 15 | 21 | 3 | 4 | 8 | Index case: Teacher with −ve sputum |
| *7 | 16 | 50 | 11 | 10 | 23 | Index case: child with +ve sputum. Teachers' X-ray normal |
| *8 | 16 | 34 | 11 | 7 | 15 | 4 index cases: teacher and child both with +ve sputum and 2 cases of P.T. in children who had recently left school |
| 9 | 15–17 | 71 | 26 | 15 | 31 | Index case: Teacher with +ve sputum. One child found with P.T. |

"zone of hygiene" as little can be done when a family lives in one room. New council housing estates may contain numerous tuberculous households as priority is given to such cases. In Table XV are set out some data concerning two estates in our area. Although, so far as has

TABLE XV.—DATA CONCERNING TWO COUNCIL HOUSING ESTATES

| | Estate A | Estate B |
|---|---|---|
| Date completed ... ... ... ... ... ... | 1949 | *circa* 1930 |
| Number of properties ... ... ... ... ... | 1,232 | 4,104 |
| Number of tuberculous households after 3 years ... | 140 (11%) | 75 (1·8%) |
| Total number of "tuberculous" houses to present time ... ... ... ... ... ... ... | 140 (11%) | 548 (13%) |
| New tuberculous cases per 1,000 per annum ... ... | 0·8 | 1·2 |
| Tuberculous deaths per 1,000 per annum ... ... | 0·6 | 0·4 |

been ascertained, Estate B contained comparatively few known tuberculous households to begin with, a further 187 cases were rehoused there during the succeeding eighteen years. The new cases and deaths are by no means excessive. New estates contain a large number of families with young children who, in the course of time, grow up. It has not been possible to estimate the age and sex distribution of the estate populations and for this reason Table XVI must be

TABLE XVI.—DATA CONCERNING COUNCIL HOUSING ESTATE B, RATES PER 1,000 PER ANNUM

| | New cases per 1,000 living | | | Deaths per 1,000 living | | |
|---|---|---|---|---|---|---|
| | London | Estate B | Middlesex | London | Estate B | Middlesex |
| 1931–33 ... ... | 1·38 | 0·51 | 1·03 | 0·79 | 0 | 0·59 |
| 1934–36 ... ... | 1·34 | 1·27 | 0·97 | 0·76 | 0·04 | 0·57 |
| 1937–39 ... ... | 1·28 | 1·21 | 0·97 | 0·68 | 0·50 | 0·48 |
| 1940–42 ... ... | 1·66 | 1·44 | 1·23 | 0·89 | 0·89 | 0·58 |
| 1943–45 ... ... | 1·78 | 1·47 | 1·36 | 0·74 | 0·60 | 0·49 |
| 1946–48 ... ... | 1·59 | 1·31 | 1·22 | 0·58 | 0·57 | 0·38 |
| 1949–51 ... ... | 1·56 | 1·13 | 1·12 | 0·39 | 0·37 | 0·27 |

interpreted with extreme caution as the proportions quoted are crude rates. The figures for London and Middlesex are taken from the reports of the respective County Medical Officers. It is interesting, but possibly without significance, to observe that the deaths seem to follow the pattern of London, the area from which the estate inhabitants have come, while the incidence of new cases follows Middlesex in which county they are now living. From Table XVII it

TABLE XVII.—COUNCIL ESTATE B, RELATIONSHIP OF "INFECTED HOUSES" 1930–51

| | Next door houses | Next door but one |
|---|---|---|
| Actual ... ... ... ... ... ... ... ... ... ... | 79 | 62 |
| Expected ... ... ... ... ... ... ... ... ... ... | 65·2 | 60·9 |
| Difference/Standard Error ... ... ... ... ... ... | 1·71 | 0·14 |
| 5% level ... ... ... ... ... ... ... ... ... ... | 1·95 | |

can be seen that on this particular estate the number of next door "tuberculous" houses does not reach statistical significance. Further, as in 28 instances it is known that although next door houses contained at some time tuberculous individuals there was in fact no possible connexion between them (e.g. both were tuberculous before living on the estate), we conclude that there is no evidence of appreciable house-to-house spread of tuberculosis on this particular estate.

*Summary.*—Our findings suggest that the known case of tuberculosis can, when taught the necessary hygiene precautions, be largely neutralized as a source of infection to others; the unknown case is a great danger and is probably the cause of tuberculous infection and consequent disease in individuals soon after leaving school; the X-ray of doctors' referred cases is a very important although not the only method of discovery of these unknown cases of phthisis; there is no evidence of appreciable house-to-house spread of tuberculosis on the new housing estates we have studied.

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## Psittacosis: Recent Epidemiological Observations

By J. C. N. WESTWOOD, M.R.C.S., L.R.C.P.

DURING 1952 psittacosis, for the second time in the history of the disease, suddenly leaped from its position as something of a medical curiosity and became an immediate problem to the public health services and clinicians, and received considerable publicity in the daily press.

From the time of its earliest known recognition by Jurgesson in 1874, as a clinical entity associated with sick parrots, small sporadic outbreaks have occurred, the most notable being that in Paris in 1892 where there were 51 known cases with 16 deaths, a high fatality rate which continued to be associated with the disease until the introduction of antibiotic therapy. But in 1929–30 the whole position changed and the disease ceased to be a curiosity. The world was flooded in those years with parrots derived largely from South America where, in the Argentine, there was a very severe epidemic amongst bird dealers and the public, and what has been rather generously termed a "pandemic" of psittacosis occurred. In 12 different countries a total of 750–800 known cases occurred with a fatality rate of 18%.

Bedson, at the London Hospital, soon demonstrated that the disease was due to a filter-passing virus (Bedson, Western and Simpson, 1930) and subsequently knowledge of the disease was rapidly acquired on both sides of the Atlantic. Bedson and his colleagues worked on the

biological characters of the virus, demonstrating its life-cycle and dependence on living cells (Bedson and Bland, 1932, 1934; Bland and Canti, 1935; Bedson, 1933; MacCallum, 1936). Bedson further developed the complement-fixation test for serological diagnosis. Rivers and his colleagues in America worked out in detail the nature of the infection in various laboratory animals and showed that the probable route of human infection was by the upper respiratory tract from dust derived from the dried fæces and nasal discharges of sick birds. He showed that the mouse could be used for isolation of the virus from human sputum and that monkeys, and probably man, could be immunized by the inoculation of live virus (Rivers, Berry and Sprunt, 1931; Rivers and Berry, 1931).

Meanwhile Meyer and Eddie in California demonstrated that so far from being confined to South American parrots the disease was widespread throughout domestic aviaries and that native Australian budgerigars were also infected (Meyer and Eddie, 1933). Aviaries in Europe were later shown also to be infected (Levinthal, 1935). Following a further demonstration by Levinthal of infection in Australian parrots consigned to London, Burnet undertook an investigation of the disease in wild birds in Australia and showed that the true parrots, lorikeets and cockatoos were endemically infected. The disease was normally mild with a long carrier state. Fledglings became infected in the nest and passed the infection to their own young in the next breeding season. Occasionally in the wild, and almost invariably, as a result of insanitary conditions of transport, among captured birds, the host-parasite equilibrium was upset and highly fatal epizootics occurred (Burnet, 1935).

The work of Meyer, Eddie and Burnet showed clearly that psittacine birds the world over were a source of danger and when it was found that the fulmar petrels of the Faröe Islands were endemically infected and a source of human cases, the field widened yet further (Rasmussen, 1938; Haagen and Mauer, 1938; Bedson, 1939). Infection has now been demonstrated in at least 70 species of birds belonging to 10 different orders. So far in this country only pigeons, herring gulls, black-backed gulls, and ducks have actually been incriminated.

In spite of the fact that the infection is now so widespread amongst birds the imposition in 1930 of bans on the importation of psittacines by many countries brought the human outbreak to an abrupt end and psittacosis once more retired into obscurity. Isolated human cases continued to occur and the biggest single source of such cases was pigeons, but the disease ceased to be an important health problem.

However, in 1952, on the grounds that pigeons in this country were already infected so reimportation of the virus could do no further harm, the ban on importation of psittacines was lifted. Within two months psittacosis had re-emerged and a series of outbreaks occurred culminating in the death of a dealer in Birmingham.

In Table I the figures obtained from examination of sera at the Central Public Health Laboratory in 1952 are compared with those of the previous two years. In Table II is shown the change in the distribution of bird and animal contacts. In the latter table is given the history of association and this does not necessarily imply a causal relationship. It is not known, for instance, whether cats or dogs can transmit viruses of this group, though one of the group is responsible for epizootic pneumonia in cats.

These figures make it clear that birds of the psittacine family constitute a far graver threat to their human associates than do the endemically infected native birds. The reason for this is probably twofold. Firstly the parrot is a domestic pet usually in intimate contact with the family. Secondly cases are nearly always associated with sick birds recently purchased, birds in fact which must be shedding huge quantities of virus so that their human contacts are exposed to very

TABLE I.—SEROLOGICAL EVIDENCE OF PSITTACOSIS

| | July 1949 – June 1951 | 1952 |
|---|---|---|
| Upper respiratory infections. Sera examined ... | 1,660 | 1,251 |
| Positive to psittacosis-LGV (titre 1/40 or rising) | 36 | 52 |
| Percentage positive ... ... ... ... ... ... ... | 2·2 | 4·2 |

TABLE II.—ANIMAL AND BIRD CONTACTS OF POSITIVE CASES

| | 1949–51 | 1952 |
|---|---|---|
| Pigeons ... ... ... ... ... ... ... | 12 | 3 |
| Chickens ... ... ... ... ... ... ... | 5 | 2 |
| Blackbird ... ... ... ... ... ... ... | — | 1 |
| Sick cats ... ... ... ... ... ... ... | — | 2 |
| Healthy dog ... ... ... ... ... ... | — | 2 |
| "Many birds" ... ... ... ... ... ... | — | 1 |
| Budgerigar ... ... ... ... ... ... ... | 1 | 13 |
| Parrot ... ... ... ... ... ... ... ... | 1 | 17 |
| No history of contact ... ... ... ... | 17 | 11 |
| | 36 | 52 |

heavy doses in the dust disturbed from plumage and the floors of cages. The rarity of man-to-man spread of the disease strongly suggests that such large doses are, in fact, necessary in order to establish infection. Prolonged intimate contact with sick birds other than psittacines is unusual except in the case of pigeon-fanciers, and even then the contact is not likely to be so close.

Although man-to-man spread of the disease is rare there have been in the past some severe and highly fatal epidemics of this nature and in nearly all the reported cases the outbreak has first involved the nursing and medical staff directly responsible for the treatment of the first case. One such outbreak in Louisiana led to disease in 19 hospital contacts with 13 deaths. In some of these outbreaks it has not proved possible to trace the origin of the first case back to a bird and the suspicion has arisen that there may be human strains of the virus which have adopted man as their primary host. To establish such a contention with any certainty is, of course, extremely difficult, but it is interesting to note in Table II the number of cases who denied any contact with animals or birds. Viruses belonging to the same group have now been isolated from pneumonia in mice, meningo-encephalitis in opossums, pneumonia in cats, enteritis in calves, infectious abortion in ewes, and lymphogranuloma venereum in man. Thus the viruses are widely distributed throughout the mammalian as well as the bird kingdom and it is not *a priori* improbable that "humanized" pneumonia strains may exist—or may come to do so in the future. Work on this problem is greatly hampered at present by the absence of any criterion by which strains of virus of different origins may be distinguished with certainty, but the problem itself is biologically an interesting one and from an epidemiological point of view its implications could be far-reaching.

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# Section of Laryngology

President—J. P. STEWART, M.D., F.R.C.S.Ed.

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## DISCUSSION ON THE EARLY DIAGNOSIS OF NASOPHARYNGEAL CARCINOMA

**Dr. William Gooddy:** Any neurologist addressing laryngologists needs to justify his presence when the subject under discussion is "The Early Diagnosis of Carcinoma of the Nasopharynx". He may try to do this in one of several ways:

(1) By showing a relative frequency of the disease in neurological practice compared with laryngological.

(2) By producing new information on symptomatology or diagnosis.

(3) By suggesting that neurological *symptoms* rather than signs are often pointers to diagnosis at a relatively early stage when treatment has a chance of good effect.

I should like to discuss these three points in turn:

(1) *The frequency of the disease.*—In assessing the frequency of the disease from previous studies, the figures of Gardham (1930), or Davis (1947) more accurately indicate the chances of seeing a case than those of Godtfredsen (1947). Gardham (1930) discussed the problem from many aspects but he was concerned with only 9 cases of malignant disease not mainly carcinomatous, collected from the records of University College Hospital.

Davis had in his records for twenty-five years only 34 cases of malignant disease of the nasopharynx, of which 19 were carcinomata. Ormerod (1951) quoted 6 cases. Godtfredsen (1947) said that the condition is "by no means rare"; but he had made a special search to find some 2,000 cases in the literature, and 454 in four Scandinavian radiological clinics over a ten-year period. Several of my figures have been derived from his observations, which were published in a monograph (1944).

Walshe (Diseases of the Nervous System, 1952) gives the condition a brief mention as a cause of facial pain.

From the records of the National Hospital, Queen Square, for four years up to 1952, only 7 *verified* cases were obtainable. These were detected out of about 35,000 patients. An incidence of 1/5,000 in-patients attending hospital with a high proportion of symptoms about the head is therefore something of an indication of rarity. The condition does, however, seem to be more often recognized.

There is something to be learnt from these figures. There are *in the end* quite large numbers of cases needing treatment, yet there are few cases found early. We cannot escape the conclusion that there is a delay in diagnosis, and neurologists at any rate are probably missing early cases. One reason for this is failure to recognize the need for proper nasopharyngeal inspection in cases of obscure facial pain.

(2) *Symptomatology and diagnosis.*—The initial symptoms appearing in Godtfredsen's (1947) 454 cases (eleven months before diagnosis was made) have been grouped by him under four headings:

| | | | |
|---|---|---|---|
| (i) Ophthalmo-neurological | (16·0%) | (iii) Otological | (23·0%) |
| (ii) Rhinological | (30·8%) | (iv) Metastatic cervical glands | (32·6%) |

*Glandular symptoms* (32·6%).

By the time that there is enlargement of the cervical lymphatic glands there must be considerable malignant spread, and adequate treatment of the initial lesion *may* be out of the question. One must in this connexion remember Gardham's point about the effect of sepsis in addition to neoplasia. Such sepsis may make the clinical state appear worse than it really is, and it may respond well to treatment. The neoplastic lesion may still be relatively small and circumscribed.

*Otological symptoms* were first to be noticed in 23·0%. These are usually due to spread of growth to involve the eustachian tube. Obstruction may lead to unilateral deafness, associated with pain.

*Rhinological symptoms* were the first to be noted in 30·8%. Palatal bulging or weakness, epistaxis or blood-stained mucous discharge are all-important. It is notable how often dental, nasal or sinus operations have been carried out for relief of painful symptoms in patients who proved later to have new growths.

*Neurological symptoms* 16·0%.—In Godtfredsen's 454 cases neurological symptoms, initially, were least common. In Davis's cases neurological symptoms occurred first in 6 out of 19 cases, that is to say in about 30%. In Godtfredsen's cases the onset of symptoms was from eleven months to four years before the diagnosis was proved. He made the important point that in nearly all cases there was *but one* neurological symptom at the beginning. He felt that neurological symptoms and signs appeared early, and not only in advanced stages of the disease, as had been previously thought.

Of neurological symptoms those referable to the V nerve are commonest for obvious reasons, for any ulcerative or neoplastic process may give rise to pain from nerve endings in the tissue where it starts. With carcinoma of the nasopharynx some fibres of the V nerve must be affected, and pain begins. It is at this stage that attention is paid to teeth, sinuses, and ears by otorhinolaryngologists, and to possible carotid aneurysms, posterior fossa lesions, trigeminal neuralgia and even depression by neurologists. *It wou'd be a real advance* if we could force ourselves each time to add to this diagnostic list the nasopharyngeal carcinoma. Admittedly we should often be wrong, and we might over-investigate a few patients, but we can develop good judgment in the use of investigation only from experience.

Whatever other symptoms or signs are added, the trigeminal ones persist, and are present in at least 70% of all cases.

With spread of the growth, evidence of trigeminal neuritis may become apparent, with the development of sensory signs. The motor root is not commonly affected.

In one of my National Hospital cases, the patient, when first seen in October 1951, had had tingling and numbness over the left upper lip and lower part of the left nostril for four weeks. The area tested with a pin showed some decreased appreciation of pin-prick with a stinging quality not noticed elsewhere. *There were no other physical signs.* He was immediately referred to Mr. T. E. Cawthorne. X-rays showed some loss of definition of the floor of the sphenoidal sinus. A biopsy specimen on section showed itself to be a squamous-cell carcinoma. This patient was treated by radiotherapy, but later developed proptosis of the left eye, with some double vision. A recurrence had taken place in the ethmoidal region. In June 1952 he had an alcoholic injection of his left trigeminal ganglion. This injection resulted in relief of pain for only two weeks, though his face remained insensitive to pin-prick.

For the past seven months this patient has complained of continuous pain. He was seen again about three months ago, on a domiciliary visit. He had taken to his bed, and needed a good deal of morphia. His general condition was so poor that he was taken back into hospital. There he proved to be physically much better than was first expected, but he was exceedingly depressed. He had loss of superficial sensation in the left trigeminal nerve territory, but no ptosis or diplopia. He developed a corneal ulcer which needed tarsorrhaphy. At present, though he has gained some weight, and is not needing much in the way of analgesics, he is so preoccupied with his symptoms and his whole illness that leucotomy is contemplated.

Lesions of the oculomotor nerves are about as common *in the end* as the trigeminal symptoms, and are usually co-existent, but *at the onset* are seen only one-fifth as often as trigeminal lesions. The oculomotor lesions thus are seen very steadily to increase the further the case develops.

The commonest disturbance comes from involvement of the VI nerve; the patient will complain of blurred or double vision, on lateral gaze to the side of the lesion. The III and IV nerves are involved less often. Nystagmus is not seen. Horner's syndrome, due to paralysis of the sympathetic fibres, is considered by some authorities as an important early sign of the disease. Unfortunately it may be due to involvement of the cervical sympathetic trunk by glands in the neck. Occasionally bilateral symptoms are seen. They are said to be due, chiefly, to oculomotor nerve lesions. In addition to oculomotor symptoms and signs, there may be displacement of the eyeball in its socket, with exophthalmos and diplopia. The optic nerve is sometimes involved, either by direct pressure or by affection of its blood supply. Optic atrophy is to be expected, but I have not seen or read of this. The lower cranial nerves are involved at some stage in about 20% of cases, and Godtfredsen has noted an interesting syndrome of trigeminal neuritis (due to lesions in the neighbourhood of the cavernous sinus) with a XII nerve palsy (due to retropharyngeal gland pressure near the hypoglossal canal), the intervening five cranial nerves being spared.

*Differential diagnosis of neurological symptoms*, with special reference to the condition labelled "atypical facial pain". The laryngologist and neurologist are frequently required to assist patients suffering from pain in the face.

If the *paranasal air sinuses* are normal, teeth may be at fault. *Teeth* may give rise to face or head pain, not only locally but remotely. The late Sir Hugh Cairns remarked that a patient on his waiting list for exploratory craniotomy was cured by Mr. Wilfred Trotter by removal of a wisdom tooth.

Patients with face pain are most commonly referred with the suggestion of *trigeminal neuralgia*. Trigeminal neuralgia may rarely occur in younger people as a symptom of disseminated sclerosis. Usually it occurs late in life, and there are certain essential features in the diagnosis (*see* Penman, 1950).

(i) Sudden "electric" stabs of pain with freedom between the stabs.

(ii) Unilateral incidence of the pain.

(iii) Specific precipitants, such as light touch of fingers, or facecloth or cold wind; talking, chewing, laughing, sneezing, or even fright may provoke a spasm.

(iv) Trigger points, stimulation of which will set off the pain, occur usually near the angle of the mouth, or nostril.

(v) Absence of objective physical signs.

*Glossopharyngeal neuralgia* is a good deal less common. The pain is deep in the throat or upper neck, and is precipitated by swallowing.

A pulsating fusiform *aneurysm on the circle of Willis* may give rise to deep-seated boring or throbbing pain, sometimes with toothache-like symptoms. The condition may cause some difficulty for those on the alert for an early nasopharyngeal carcinoma. It can only be confirmed by the presence of an intracranial bruit (which is uncommon) or by arteriography.

*Migraine* may show itself not as the usual triad of visual blurring or hallucinations, headache and nausea, but as local dull pain in the region of one or other eye, with lacrimation and suffusion of the conjunctiva. Previous ordinary migraine, a family history and response to specific treatment, may be of diagnostic assistance.

*Depression* with the physical symptoms of face pain is most important, but often goes unrecognized. The patient, usually a woman in her fifties, may have undergone much medical or surgical treatment fruitlessly. The condition responds magically to electric convulsant therapy.

*Coronary artery disease* once, in my experience, presented as facial pain alone. The relationship to exercise was obvious from a few leading questions. Mr. C. S. Hallpike has told me of a case of peri-arteritis nodosa with nasopharyngeal symptoms.

*Secondary carcinomatous deposits in the skull base* may also cause facial pain.

In New's (1922) 79 cases of malignant pharyngeal growths no less than 74 had had operations for symptoms before diagnosis was made.

The history, with clinical examination and appropriate investigations often enables us to make a correct diagnosis. Appropriate treatment may then follow. When diagnosis continues to elude the neurologist there should, I feel, be a specific mental reaction, that the case may be one of early carcinoma of the nasopharynx.

(3) Neurological *symptoms* rather than physical signs may indicate the disease at a *curable* stage. Neurological signs, though invariably present later, may not be present early in more than 30% of cases. Of course, symptoms may also not be present early. Some patients will therefore be luckier than others in the evolution of their illness, in the same way that, for example, a patient with mild pulmonary tuberculosis is fortunate in having early hæmoptysis leading to early diagnosis of his condition. *Symptoms without objective signs must therefore be regarded always with the greatest suspicion.*

Our aim should be to diagnose carcinoma of the nasopharynx when symptoms are still unassociated with signs of spread. Therefore:

(i) The most important symptom is obscure pain in the face.

(ii) The absence of physical signs and positive routine investigation is *not* a difficulty in diagnosis of the cause of facial pain, but a strong pointer in the direction of an early carcinoma.

(iii) An expert opinion on the state of the nasopharynx is essential, once the possibility of a growth occurs to us.

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**Mr. Terence Cawthorne:** I agree with Dr. Gooddy that when confronted by a patient complaining of continual pain in one side of the face who may also have some weakness of the ocular muscles or deafness on the same side, one is not satisfied until the nasopharynx has been thoroughly examined. I am often far from happy during the process of examining the nasopharynx of these patients, because I am never quite sure whether I shall be able to get a really satisfactory view of the whole nasopharynx. In particular I find that the highest part of the postero-lateral wall is elusive and I believe that it is from just this area that many growths originate.

The clinical picture presented by a malignant growth in this situation is a moving picture in which the predominating feature in the early stages may be succeeded by other and entirely different features as the disease spreads.

Godtfredsen (1944) drew attention to this in an extensive investigation into the symptomatology of malignant nasopharyngeal growths.

He grouped the symptoms into neuro-ophthalmological, glandular, nasopharyngeal and otological. Having noted the incidence of the initial symptom reported in the literature he compared this with the pattern of the well-established disease (Table I).

TABLE I.—PRESENTING FEATURES IN MALIGNANT DISEASE OF THE NASOPHARYNX (GODTFREDSEN, 1944)

| | Initial symptom | Symptoms in established disease |
|---|---|---|
| Neuro-ophthalmological .. .. .. .. .. .. | 33·5% | 38·8% |
| Glandular .. .. .. .. .. .. .. .. | 26·1% | 70·0% |
| Nasopharyngeal .. .. .. .. .. .. .. | 24·1% | 40·0% |
| Otological .. .. .. .. .. .. .. .. | 15·4% | 49·0% |

It will be appreciated, of course, that whereas in the first column we are dealing with one symptom only, in the second column two or more symptoms may have been included. This table indicates that a neuro-ophthalmological disturbance is often the first warning, and that it is only as the growth extends that the other and more obvious features come to the forefront of the picture.

As much of my work is at a neurological hospital it is not surprising that I should see patients in whom the initial and predominating symptoms have been neuro-ophthalmological, but what impressed itself on me so much is the fact that these are often the earliest symptoms.

In the 11 cases of carcinoma of the nasopharynx which I have seen in recent years the initial symptom has been neurological in 10, although not all were seen at Queen Square (Table II).

Table III gives the symptoms the 11 patients presented when I first saw them.

TABLE II.—INITIAL SYMPTOM IN 11 CASES OF CARCINOMA OF THE NASOPHARYNX

| | Cases |
|---|---|
| Facial pain .. .. | 8 |
| Horner's syndrome .. | 1 |
| Diplopia .. .. .. | 1 |
| Deafness .. .. .. | 1 |

TABLE III.—PRESENTING SYMPTOMS IN 11 CASES OF CARCINOMA OF THE NASOPHARYNX

| | Cases | | Cases |
|---|---|---|---|
| *Neuro-ophthalmological* | 11 | *Nasopharyngeal* | 3 |
| Facial pain .. .. | 8 | Obstruction .. .. | 1 |
| Diplopia .. .. | 5 | Catarrh .. .. .. | 1 |
| Horner's syndrome .. | 2 | Bleeding .. .. .. | 2 |
| Ptosis .. .. .. | 1 | *Cervical glands* | 4 |
| *Otological* | 5 | Palpably enlarged .. | 4 |
| Deafness .. .. | 5 | Visibly enlarged.. .. | 0 |

This small group of patients behave in a similar manner to the large number reported by Godtfredsen: namely the earliest symptoms are usually neurological. This is due to implication of certain cranial nerves in the region of the base of the skull. It is only as the growth spreads downwards that the other symptoms appear.

*Methods of examination of the nasopharynx*, including the removal of pieces of tissue for biopsy.

*Palpation.*—This uncomfortable method of examination calls for experience and dexterity on the part of the examiner, and a certain amount of co-operation on the part of the conscious patient. It is quite effective for large growths which extend well forwards and downwards into the nasopharynx and which, incidentally, can usually be readily recognized by sight. For small growths high up on the lateral pharyngeal wall, from which site so many of these growths seem to originate, this method suffers from the great defect that our finger nails are the wrong way round; so that the very area which we want to touch comes up against the surface of the nail. It is true that the edge of an ulcer can sometimes be recognized by the experienced finger tip, and certainly an ulcerating area can be encouraged to bleed; though in the struggle that often accompanies this manœuvre normal mucosa may also bleed. I must admit that despite quite a lot of practice, I still find it difficult to be sure of what my index finger is feeling when I get it into the nasopharynx. Perhaps this is because I only resort to palpation when I am unable to see anything by the other methods which we will now consider.

*Post-nasal mirror.*—This method usually gives a good view of the posterior nares, and of the vault and lateral wall of the nasopharynx. The highest part of the posterior wall, however, cannot be seen face on in the mirror, but only in profile. With the patient in the position of choice for using the post-nasal mirror it will be found that the highest part of the posterior nasopharyngeal wall slopes backwards, and so a growth in this region can be easily overlooked. There is, of course, too, a certain proportion of patients who will not relax sufficiently to allow a satisfactory view. In such cases and in the presence of suspicious symptoms, repeated examinations may be needed before a negative report can be considered. If there is any doubt, however, some of the remaining methods to be described should be employed.

*Nasopharyngea' speculum.*—The direct speculum of Yankauer is the one in general use and it can be inserted after suitable local medication without a general anæsthetic. With it a view is afforded of the side wall and most of the posterior wall of the nasopharynx, and it allows a good direct view when taking a piece of tissue for biopsy. The area which it can reach is, however, limited and some experience is necessary in recognizing the normal.

*Nasopharyngoscope.*—Most nasopharyngoscopes are made so as to pass through the nose and, in consequence, are limited in the size of the field given by the tiny mirror. In most, the field illuminated is either at right angles or at an acute angle to the shaft of the instrument. This gives an excellent view of the vault and side wall of the nasopharynx and in particular of the pharyngeal orifice of the eustachian tube. It has, however, a blind spot, again in the most important part of the field, namely the postero-lateral aspect of the nasopharynx. Other and larger nasopharyngoscopes are sometimes used through the mouth, but here again it will be found that in most, if not in all, the vital postero-lateral wall is left out of the picture.

Last year the late Mr. Schrantz of the Genito-Urinary Mfg. Co. designed for me a lighted speculum (von Eicken) in which the light was in a post at right angles to the shaft so that an area in front of and above the shaft of the 'scope was illuminated. With mirrors at different angles every area of the nasopharynx can be illuminated and viewed in turn. This should be a valuable additional method of examining the nasopharynx.

*X-rays.*—Every patient in whom a nasopharyngeal growth is suspected should have an X-ray of the base of the skull and a lateral view to show the soft tissue outline of the nasopharynx. The basal view may show a cloudy area in the region of the basal foramina, while the lateral view may reveal a soft tissue swelling; these two views will, between them, often give the most valuable information and they should be part of the routine examination of every patient suspected of having a nasopharyngeal growth.

*Examination under anæsthetic.*—With the patient under a general anæsthetic it is possible to examine more leisurely and more fully the nasopharynx either with a mirror or by means of a direct speculum and also to take a piece of tissue for biopsy. In doubtful cases it is often wise to carry out such an examination without undue delay.

There remains the method of direct exposure by splitting the palate as described by Mr. C. P. Wilson (1951). That this method offers an excellent exposure of the nasopharynx I know, because I have had the opportunity of seeing Mr. Wilson do this operation on 3 cases. In at least 1 other of which I have personal knowledge, I believe that only this method would establish the diagnosis, because Mr. Wilson has told me that even with the excellent direct view that he had, no definite growth could be seen, but a biopsy from the area under suspicion showed that a growth was present.

I would like to say how very much I appreciate the way in which Mr. Wilson and our colleague Mr. Douglas Ranger have always come to my assistance with these difficult cases.

Other nasopharyngeal growths which may behave like carcinoma in that they cause cranial nerve palsies are plasmocytomas or chordomas. In each of these growths which I have seen the tumour has been slow growing and widespread involving several cranial nerves. Another case whom I saw at King's College Hospital with my colleague Mr. R. S. Lewis eventually proved to be a simple cyst.

I have found that the diagnosis of carcinoma of the nasopharynx is often difficult particularly in its earliest stage. And yet it is at this early stage that we must make the diagnosis if treatment is to have a chance.

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**Professor R. McWhirter:** The prognosis is good when nasopharyngeal tumours are treated at an early stage but, unfortunately, they are often so advanced by the time they are referred that treatment must be palliative. There is no doubt that the overall survival rate could be raised considerably if delay could be reduced. It is important to enquire into the cause of this delay for many of the patients are young and would otherwise have a good expectation of life.

Analysis of over a hundred case records shows that the average delay from the time of onset of symptoms to treatment was 9·5 months. The average delay on the part of the patient was only 1·7 months. The average delay on the part of the medical profession was 7·8 months. Those who advocate cancer propaganda to the public would probably be less enthusiastic if they enquired a little more fully into the cause of delay. Clearly before there is any propaganda to the public, the medical profession must be educated to recognize malignant disease at an early stage.

In view of these remarks it becomes our duty to enquire into the reasons why nasopharyngeal tumours are so often overlooked. In general it may be said that the less commonly occurring diseases are associated with the greatest delay in their recognition. Nasopharyngeal tumours represent only 0·2% to 0·3% of all cases of malignant disease. A little simple arithmetic shows that only one general practitioner in sixty will see a new case of malignant disease of the nasopharynx in any one year. It is not surprising therefore that when a general practitioner does see a patient with a malignant tumour of the nasopharynx he will fail to recognize it. His failure is all the more understandable when it is recalled that during his period of training as a medical student he may never have had an opportunity of seeing a case. If he should have been fortunate enough to have seen even one case, it is highly probable that the disease was advanced with all the so-called "classical signs" already present. Textbooks, which tend so often to portray the terminal stages, will not be of great assistance to him in the recognition of a treatable case.

Even amongst the members of the staff of a hospital it is surprising to find that the correct diagnosis may not be reached even in advanced cases. Again this may be explained by lack of experience, for, in a hospital serving a population unit of, say, one million only about 6 new cases will be referred each year. Many members of the staff may see no more than one or two cases during their complete term of office.

On looking through the case records we have found that patients are referred to a wide variety of specialists.

If the presenting feature is glands in the neck, the patient is commonly referred to a general surgeon. In a young patient a diagnosis of tuberculous glands may be made and the patient's name placed on a long waiting list. Even where a gland has been excised and shown to be malignant, the primary tumour may still be overlooked, for a histological report of lymphosarcoma or reticulum-cell sarcoma is often interpreted as denoting that the glands are the primary site of the disease.

We found, too, that patients may be referred to a physician when diplopia is the presenting sign. In some of these cases a diagnosis of disseminated sclerosis may be made while in others the diagnosis has been basal encephalitis.

Should the tumour extend into the orbit and give rise to proptosis the patient may be referred to an ophthalmologist under the impression that the condition is a primary tumour of the orbit.

Pain in the second division of the trigeminal nerve not infrequently resulted in the patient being referred to a dentist for extraction of teeth.

Surprisingly enough we found that only a limited number of patients were referred in the first place to the otolaryngologist. It is clear, therefore, that the general practitioner in many instances did not even suspect the presence of a tumour in the nasopharynx when he referred the patient to hospital. The presenting features in the patients referred to the otolaryngologist were nasal obstruction, blood-stained nasal discharge and deafness. In young patients the clinical picture may suggest merely hypertrophied lymphoid tissue in the nasopharynx and some patients had their tonsils and adenoids removed without the true nature of the condition being recognized. Others received treatment for some time for otitis media or had their middle ear inflated. A small tumour mass in the nasopharynx is difficult to recognize by indirect examination and this is particularly so when the surface of the tumour is not ulcerated. It is not always easy to obtain a portion of tumour tissue for histological confirmation and delay has occurred in some cases because a negative biopsy was obtained in the first instance.

The general impression gained was that the otolaryngologist too often confined his attention to the nasopharynx and failed to carry out a more general examination. The other specialists noted the neck glands and the ophthalmo-neurological signs but did not appreciate that the cause might be in the nasopharynx and, in consequence, the nasopharynx was never examined.

In a considerable number of cases the correct diagnosis was not established until the patient was referred to the Radiotherapy Department. In the recognition of nasopharyngeal tumours the following points are helpful:

Secondary spread to the glands of the neck is common in nasopharyngeal tumours and often occurs at a very early stage. The glands first involved usually lie deep to or slightly posterior to the upper end of the sternomastoid. The main direction of spread is then down the posterior cervical chain which lies along the anterior border of the trapezius. It is uncommon to find this distribution of glands in any other disease although occasionally the same distribution may be found in tuberculous lymphadenitis.

Palpation of the nasopharynx with the finger is often of great value. We find it best to palpate the nasopharynx through the soft palate.

Radiographic examination will, in 90% of cases, help to determine whether a tumour is present in the nasopharynx and also to assess its extent. The examination must, however, be carefully conducted, and where a nasopharyngeal tumour is suspected the diagnostic radiologist should be informed of this and requested to make the appropriate examination.

A lateral radiograph of the nasopharynx gives much valuable information. The exposure required is approximately the same as that for the cervical spine. The lateral soft tissue view, so valuable in the lower pharynx, is insufficiently penetrated but the relative positions of the film and tube are the same. If the tumour fills the nasopharynx or arises from the anterior or posterior walls of the nasopharynx, it will be well demonstrated.

If, however, the tumour is small and arises from either lateral wall, its outline will not be seen and all that may be detected is a slight increase in the density of the nasopharynx. A view of the base of the skull will demonstrate these laterally placed tumours more satisfactorily for they can now be seen extending into the air space of the nasopharynx. Erosion of the base of the skull may be demonstrated and the posterior margin of the greater wing of the sphenoid should be examined with particular care.

Where the tumour has extended into the orbit the usual "chin-nose view" often shows no evidence of erosion of bone. The tumour appears to extend along the inferior orbital fissure. This view may help where the tumour has extended into one or other antrum.

Where there is no bone destruction it is not always possible to determine whether the soft tissue swelling in the nasopharynx is a tumour or merely a mass of hypertrophied lymphoid tissue. The difficulty arises mainly in children and radiographic examination, while of great value, must be supplemented by the clinical and histological information.

When instruction is being given to medical students the lecturer should bear in mind that it may be a very long time before any of his students will encounter a case. His description should be simple and confined to essential points—histology and treatment should be dismissed in single sentences. The student should be given the opportunity of examining at least one case and preferably an early case, and he should be taught the value of digital and radiographic examination of the nasopharynx.

Because radiotherapy is the accepted method of treatment the radiotherapist is the clinician in the hospital with the greatest experience of this type of tumour. He should be consulted in all suspicious cases at the earliest possible stage.

It is all-important to reduce the period of delay in diagnosis. As radiotherapists we have to bear the burden of treatment of many cases which are referred too late. We ask to be consulted at the earliest possible stage because we believe we can be of assistance in establishing the diagnosis.

**Mr. C. P. Wilson** said that he agreed with Dr. Gooddy that V nerve pain, particularly 2nd division, was by far the most common early neurological symptom, but he had not stressed an important early physical sign—namely numbness in part of the area supplied by the nerve. Pain was presumably an indication of irritation but if there was loss of sensation it was an indication of pressure and it was then doubtful if the case could be called early.

There were sarcomata, lympho-epitheliomata, squamous carcinomata and so on with primary growths in the nasopharynx and glands in the neck, but beyond all these there was a type of case which he might call X. He did not know what X was but some of the cases Mr. Cawthorne had been talking about were of this rather worrying type; cases in which there did not appear to be a primary growth in the nasopharynx or at any rate not for a long time after symptoms and other physical signs had been present—sometimes months and even years.

It had always been said that the primary growth must be very small and had been missed and Mr. Cawthorne rightly stressed the importance of careful examination of the nasopharynx, but in this type of case there really was nothing to be seen in the nasopharynx.

He had on several occasions done a transpalatal exploration by the method he had described in 1951 (*Proc. R. Soc. Med.*, **44**, 353) and had found nothing on direct vision or occasionally nothing more than slightly suspicious swelling of the posterior wall. In these cases, it was his practice to remove a slice of tissue $\frac{1}{8}$ in. wide and $1\frac{1}{2}$ in. long from the posterior wall behind the eustachian cushion going right down to the prevertebral fascia and in such cases histological examination showed a squamous-cell carcinoma in fibrous tissue.

In these cases, as Mr. Cawthorne had said, the earliest symptoms were neurological or glandular, or possibly aural and there were no physical signs of growth in the nasopharynx. Unilateral persistent pain of the 2nd division of the V nerve without obvious cause was suspicious and if it was combined with numbness or with some other sign such as VI nerve palsy the diagnosis of carcinoma was almost certain.

Here was a condition in which there might have been varied symptoms for months or years, or glands had been removed and no primary growth found. He had had one case in which nothing had appeared in the nasopharynx until five years after glands had been excised and a course of post-operative radiotherapy given, and other cases where nothing had appeared for two or three years after excision of glands and no radiotherapy. He felt it impossible to look upon these cases as primary growths of the nasopharynx. The signs and symptoms were grouped in a circle around an area just outside the lateral recess. The commonest early symptoms were those of extension upwards through the foramen lacerum and with involvement of the V and VI nerves—others were eustachian tube involvement or lateral extension to glands or even vagus nerve, while yet others were associated with extension towards the nasopharynx and eventually its mucosa.

This seemed to be a condition in which a primary growth started *outside the nasopharynx* and only secondarily invaded it at a later stage. One had the same sort of problem with glands lower in the neck where the primary growth was reputed to be a small undiscovered focus in the pyriform fossa. Œdema of the lateral wall of the pyriform fossa associated with a mass of glands contiguous to it did not mean there was a primary growth in the fossa and in many cases at autopsy it was quite impossible to separate the gland mass from tumour invading the pyriform fossa. The old suggestion that some of these cases were really primary branchial carcinomata might be correct, and if so it was also possible that these puzzling cases outside the nasopharynx might have a similar origin. Where did the 3rd and 4th branchial clefts open? The anatomists talked vaguely about the thyroid cartilage but this had no particular developmental connexion with any special area of mucous membrane. The second cleft, certainly in his experience, almost invariably opened in the middle of the posterior pillar of the fauces and could not the third cleft open behind this in the lateral recess? If so it was possible that these cases were really branchiogenic carcinomata of the third branchial cleft.

**The President** said that recently he had seen a case in which there was ulceration of the nasopharynx where the features were those of specific disease and where the blood Wassermann reaction was strongly positive. The patient was then turned over to the Venereal Disease Department for treatment, but some weeks later, as the local condition had deteriorated and some enlarged glands had appeared, he was sent back for a further opinion. Some tissue was removed for biopsy and the report came back positive for nasopharyngeal carcinoma. One therefore had always to keep in mind the possibility of these two conditions being present at the same time.

He asked whether the plane of the choanæ altered with age as a short time ago he had performed a transpalatal approach for an atresia of a choana in a young boy and had experienced difficulty in obtaining a good exposure of the choanæ, whereas he had found on former occasions an excellent view of the choanæ in adults. He thought that maybe with age the plane of the choanæ altered.

**Mr. G. H. Howells** gave some figures of cases seen since 1947 at the Royal National Throat, Nose and Ear Hospital. They had had 19 cases through their hands, belonging to age groups between 25 and 79. Of these the first symptom complained of in 5 cases was obstruction. In only 1 case was it deafness. The first complaint was ophthalmological in 6, and V nerve pain in 3. The duration of the first symptom before they came to the department was between three and eight months. 14 complained of previous symptoms; 3 had glands in the neck, and 1 a secondary deposit in the sternum. This last had also a secondary deposit in the lung. Survival after treatment varied between three months and five years. The longest survival was in a comparatively young subject in whom clinically the condition was most advanced. The only really early case was in an elderly patient who complained of a minor degree of deafness in one ear. This could not have been due to any mechanical obstruction as the tumour was very small and had not involved the eustachian cushion.

Their first attack should be by way of propaganda amongst general practitioners in order that they might send their patients to them earlier. But he agreed with Mr. Wilson that one saw many cases in which one was morally certain that there was an underlying growth, but one watched them for a very long time before anything was apparent.

**Mr. E. D. D. Davis** said that he believed Mr. Wilson was referring to a type of growth which originated in the body of the sphenoid, crept along the base of the skull and presented itself in the nasopharynx. He had seen two post-mortems of this type of case. As expected, the neurological and ophthalmological signs appeared too late.

If a biopsy was necessary it was preferable to obtain it through Mr. Wilson's transpalatal incision.

**Mr. F. C. W. Capps** said that he could not help feeling that they should be a little kinder to the general practitioner. He was forever being urged to diagnose more and more, earlier and earlier. The people more concerned were those to whom the practitioner sent the cases with persistent symptoms for which he could find no cause, and which he was unable to alleviate. It should be the business of the Ear, Nose and Throat, the Dental and the Neurological Departments to discover the underlying cause. These growths were obviously of two types. When in charge of a reception area with a population of anything up to 200,000 one had a good opportunity of seeing these types in fairly definite proportions. In one of them the growth filled the post-nasal space, and in the others there was infiltration without very obvious invasion of the space. The possibility of an embryological origin as suggested by Mr. Wilson was of interest. Histologically there were many different types of tumours in this region. Epithelial, connective tissue, and endothelial tumours all occurred, and it would be difficult to ascribe a common origin to them all. Trotter, W. (1911, *Brit. med. J.*, ii, 1057) described these tumours and their symptomatology and called them endotheliomata; he described an early irritation of the muscles of the palate which sometimes resulted in spasm and an elevation of the palate on the side affected. This sign had been seen in 2 of Mr. Capp's own cases.

**Mr. Cawthorne,** in reply, said that it was the rhinologists themselves who must look into this problem of the early diagnosis of carcinoma of the nasopharynx. Many of the cases he had seen had previously been submitted to rhinological examination with negative results, and he could recall only too vividly cases which he had himself overlooked. These cases of early carcinoma of the nasopharynx were difficult to see and rhinologists must make use of every means at their disposal of examining the nasopharynx in a case suspected of having a growth.

He could assure Mr. Capps that, like Dr. Gooddy, he had included only cases of squamous-cell carcinoma or lympho-epithelioma in his list.

**Professor McWhirter,** in reply to Mr. Wilson on the question of unulcerated tumours, suggested that the following explanations should also be considered:

(1) A number of tumours of the skin began subcutaneously and it was therefore to be expected that some tumours of mucous membrane origin should begin submucosally.

(2) Some of the undifferentiated malignant tumours of the nasopharynx are reticulum-cell sarcomata and, as in the tonsil, these tumours may not be ulcerated in the earlier stages.

(3) The visible tumour mass may not be the primary tumour but the secondarily involved retro-pharyngeal lymph glands.

(4) A primary tumour of the sphenoidal air sinus may extend downwards and produce an unulcerated swelling of the roof of the nasopharynx.

In reply to Mr. Capps his criticism was not particularly directed against general practitioners and, in fact, had been mainly directed against those responsible for the education of medical students.

**Mr. C. P. Wilson,** in reply to the President said he thought that the position of the choanæ varied in different individuals and he did not think that it changed much during adult life.

In reply to Professor McWhirter, he said that at post-mortem he had looked carefully at some of these cases and had found nothing in the sphenoid. The growth was near the body of the sphenoid, but not actually in the sphenoidal sinus. To another remark of Professor McWhirter's as to the origin of these tumours, he found it difficult to conceive that a squamous-cell carcinoma of the mucous membrane could produce so much destruction in the bone and glands and still remain a completely unulcerated tumour.

# Section of Otology

President—Air Vice-Marshal E. D. D. DICKSON, C.B., C.B.E., M.D., F.R.C.S.Ed., D.L.O., Q.H.S.

[*March* 6, 1953]

## DISCUSSION ON TINNITUS

**Mr. R. S. Venters:** *Subjective Tinnitus or Tinnitus Aurium*

The content of this paper relates to subjective tinnitus or tinnitus aurium, for the reason that as a symptom it is common, little is known about its causation, its significance is difficult to assess and its treatment is unsatisfactory in the extreme. On the other hand, objective or vibratory tinnitus, with the exception of the vascular bruits, is uncommon: its ætiology is usually apparent, and treatment can be directed at least with the assurance that it is both scientific and practical. Tinnitus aurium is the problem and it would be best were discussion confined to that symptom.

Tinnitus needs no description and it could be classed with such symptoms as headache and pain as being of almost universal experience. The subjective noise is rarely complex; those of average intelligence have little difficulty in describing it and the uniformity of such description leaves no doubt as to its presence. To the clinician there is something abstract about tinnitus. The physical and mental dysfunctions of the body in general can be readily recognized and the presence or severity of such symptoms as pain can be assessed with a reasonable degree of accuracy. Tinnitus, however, cannot be recognized by the clinician and the associated loss of function, auditory or otherwise, which undoubtedly exists, is difficult to determine and define in any terms. With tinnitus there is distress and it may be that it is this circumstance that, in our present knowledge, concerns us most as otologists.

For a clinical investigation into tinnitus to be of value it should be confined to a clinic serving a known population; the diagnosis and treatment being in the hands of one individual; the geographical area concerned sufficiently remote to discourage further advice. For these reasons I chose my clinic in Dumfries, which serves the South Western area of Scotland and is located seventy-five miles from both Glasgow and Edinburgh. The department in Dumfries is attached to that in Carlisle.

The total population of the area is approximately 120,000, and of those 34,870 are gainfully employed. Investigation revealed that, of those employed, in 25,174 the industrial risk as to deafness was minimal and that in 9,696 there was a definite aural hazard. An aural hazard was considered to be present in such industries as boiler making, heavy engineering, sheet metal workers, mining and certain types of factories.

The clinical records for the ten-year period, 1943–1952, have been examined and of the total of 1,466 cases of deafness it has been found that 235 had associated tinnitus. There were only 19 cases of tinnitus in which no demonstrable deafness could be elicited. These figures do not include children under the age of 15, and I also omitted all cases of transitory middle-ear infection and other conditions not involving the hearing mechanism proper.

Fowler (1912) reviewed 2,000 ear cases and found that tinnitus was present in two-thirds. The same writer (1944) states that in a similar number of cases of aural disease the incidence of tinnitus was as high as 85% and I assume, perhaps incorrectly, that the incidence in both reviews relates to the same 2,000 cases. My survey placed the incidence, relative to aural disease, at only 16·5% and I would like to think that this remarkable drop is due to the progress made in the practice of otology in the past forty years. The incidence on a population basis is 0·21%.

### ÆTIOLOGY

Table I shows that, in just over 50% (129 cases), tinnitus can be attributed to middle-ear disease—which includes chronic otitis media, active and inactive, chronic catarrhal otitis media and fibroid otitis media. The last two conditions I consider as being of infective origin. One-half of the above

TABLE I.—DIFFERENTIAL ÆTIOLOGY IN 254 CASES OF TINNITUS

| | | |
|---|---|---|
| Middle-ear disease | Active 63<br>Inactive 66 | 129 |
| Degenerative deafness | | 54 |
| Otosclerosis | | 31 |
| Trauma | | 11 |
| Ménière's disease | | 9 |
| Syphilis | | 1 |
| VIII nerve tumour | | 1 |
| Anæmia | | 1 |
| Psychogenic | | 12 |
| Unclassified | | 5 |

(63 cases) showed active infection, and the other half (66 cases), clinical evidence of infection at some time or another. No case giving a history of otalgia or otorrhœa, without clinical evidence to support it, was included. If one were to exclude degenerative type deafness—and quite a proportion of these are in the old-age group—otosclerosis and trauma, the ætiological condition is overwhelmingly middle-ear infection. The table is representative of the known and common causes of tinnitus, but it by no means exhausts the list. It is perhaps, what one might expect, and the interest would appear to lie most in the relative incidence to middle-ear disease and in a given population.

There are 148 females and 106 males, and it might be assumed from these figures that the threshold of tolerance as to tinnitus was lower in the female than in the male. An assumption of this kind is probably correct for, of the 1,466 records of ear disease examined, the sex distribution was almost equal. Overall tolerance of tinnitus would appear to be low as in over 75% of the above cases the presenting symptom was tinnitus and the consultation was sought on that account. Deafness, otorrhœa and vertigo were frequently looked upon as of secondary importance.

*Incidence relative to age.*—Fig. 1 shows that the incidence goes up steeply to a maximum at the 41–50 age group and following an appreciable dip at the 51–60 age group, again rises. The female curve is similar in pattern but, in the male, the distribution is more even and this I attribute to the overall incidence of trauma which is wholly confined to this sex.

*Incidence relative to age in the three main ætiological classes*, middle-ear disease, degenerative type deafness and otosclerosis. Fig. 2 shows the large part played by middle-ear disease in the problem of

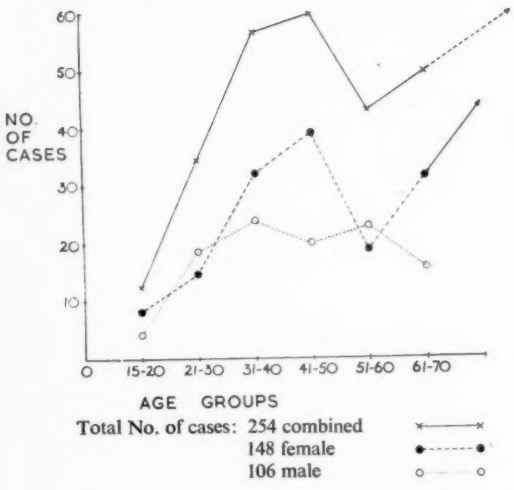


FIG. 1.—Incidence of tinnitus related to age.

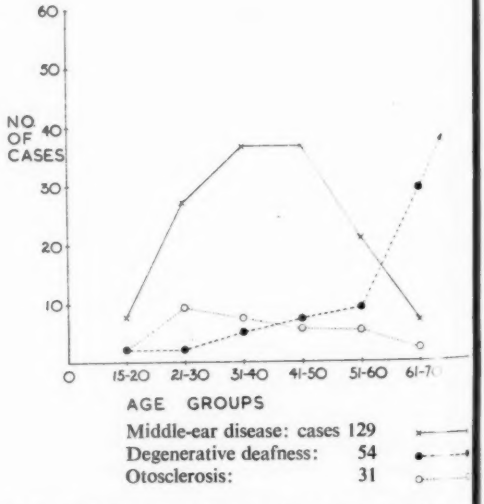


FIG. 2.—Incidence of tinnitus related to age in middle-ear disease, degenerative type deafness and otosclerosis.

tinnitus and that the incidence of this symptom is related to age at the time of its onset. The rise in the degenerative type deafness at the 61–70 age group is, of course, due to advancing years.

Closer examination of the age incidence reveals that, with the exception of aural and acoustic trauma, the late appearance of tinnitus is common to all diseases with which tinnitus is associated. The causative lesion is well established and usually irreversible before advice is sought and it is this very fact that prevents effective treatment.

In general, both from personal experience and close examination of the records, continuous tinnitus is more frequently found in old-standing inactive healed lesions and the less troublesome intermittent variety in active lesions. It is, perhaps, safe also to state that in the healed lesions the tympanic membrane is usually not perforated. Again, in the active disease, it is the tubal and the tympanic cavity infections of long standing that give rise to tinnitus and it is rare to find the symptom associated with gross lesions involving disorganization and destruction of bone. I reviewed the notes of 150 cases of chronic suppurative otitis media requiring modified or radical mastoid operation and in only 2 was there any complaint of tinnitus. Apart from these important generalizations there is a wide diversity of clinical findings, ranging from trivial scars and calcareous deposits to a chronic adhesive process in its severest form. There appeared also to be little relationship between the degree of deafness, the severity of the tinnitus and whether it was continuous or intermittent. Repeated attacks of acute middle-ear infection seem more likely to give rise to tinnitus in later life than a single destructive infection and, while middle-ear disease is largely the result of pre-adolescent infection and tinnitus a symptom associated with adult life, it is an interesting fact that an acute infection, occurring in middle or late life, frequently results in a severe hearing loss with tinnitus, out of all proportion to the clinical findings. I have noted that, should tinnitus be present during the acute invasive stage of a middle-ear infection, recurrence of the symptom is more likely many years later. It is also true that deafness resulting from uncomplicated middle-ear disease is rarely progressive, but, should there be an associated perceptive loss, further deterioration is to be expected. Different organisms have different toxic effects and the same organism has a variable virulence. Some are known to be more locally invasive and destructive than others, and it is common experience that, in general, the more invasive and destructive the less the constitutional upset. There is also the individual response to infection and the fact that with increasing age secondary toxic effects are more frequent.

With such a diversity of subjective and objective clinical findings, it is not hard to imagine a similar variation of the pathology within the tympanic cavity and to conclude that no single one in itself is the cause of the tinnitus.

Before the days of the sulphonamides and the antibiotics, I was much interested in the variable permanent loss of hearing following acute otitis media. Identical clinical findings, the same organism and a treatment procedure that was timely, uniform, and effective, resulted in a hearing loss that varied between that which could hardly be demonstrated to that which amounted to a serious disability. This wide variation was due rather to the involvement of the perceptive mechanism than of the conductive, and one could postulate that, in all infections of the middle ear, there is to a greater or lesser degree some interference with the cochlear or neural pathways.

I believe that it is this cochlear or neural involvement that determines the presence or absence of tinnitus, ten, twenty or thirty years later.

My attempt to relate industrial hazard to the incidence of tinnitus has been largely abortive. I found that the incidence was no greater in industry where I considered the acoustic hazard to be appreciable than in employment where the risk was slight. I found only 11 cases in which the onset of tinnitus could be directly attributed to trauma and I divide trauma into two groups, aural and acoustic. Aural trauma includes blast injuries, concussion and fractures involving the petrous bone: acoustic trauma, cases arising from sudden loud noise and the cumulative effect of noise over a long period. In 10 of the 11 cases the tinnitus was due to concussion, cranial fracture or blast and only in one could I attribute the symptom to the cumulative effect of loud noise. This patient was a boiler maker. In a boiler works employing some hundreds of men and, in a period of twenty years, this is the only case that has come to my notice. It may be that in industry protective measures are more effective or the ear is becoming conditioned to the ever increasing crescendo of noise to which the human being is subjected.

The tinnitus associated with sudden aural trauma can be likened to that found in the vascular incident, for the symptom is experienced immediately; the pitch and intensity rarely vary and bear little relation to the degree of deafness sustained. I have also found, in such cases, that the deafness is rarely progressive and the tinnitus never disappears. It is probable that there are no other conditions with such a similarity of clinical features associated with tinnitus, and it is reasonable to suppose that the tinnitus arises as the direct result of a traumatic lesion involving the central nuclei, neural pathways or the inner ear.

Otosclerosis, Ménière's disease and the acoustic nerve tumour are clinical entities and it would seem pertinent, for the purpose of this paper, to discuss them together. The pathology, if not the aetiology, is known and all are progressive diseases. Tinnitus is not necessarily a constant feature

and may or may not be the presenting symptom. In Ménière's disease and acoustic nerve tumour the pathological lesions involve the perceptive mechanism and in otosclerosis there is, with progression of the disease, much evidence of diminished cochlear activity. In all there is a variation in the intensity and pitch of the tinnitus, and it would appear to coincide largely with the clinical signs and symptoms of quiescence or progress. In these diseases the presence and degree of tinnitus is related directly to the severity of the other clinical features—deafness and vertigo—and it would seem unnecessary to emphasize that this feature is unusual in the consideration of tinnitus as a symptom of other disease.

I have grouped together a number of cases of deafness of neural origin and of obscure ætiology under the heading of degenerative type deafness. In quite a high proportion of these no trace of the primary cause could be found and no symptoms other than deafness presented. Of the total number of cases of tinnitus (254), 54 or approximately 20% can be included under this heading, and the graph of the incidence relative to age (Fig. 2) shows that there is a steady but slow increase until the 51–60 age group when there is a very sharp rise. The deafness is, as a rule, present for a variable length of time and the degree of loss considerable before the onset of the tinnitus. In probably no other condition is the tinnitus more variable both as to intensity and pitch. It would appear to change from day to day and even from hour to hour; it can be continuous or intermittent and for no good reason can disappear entirely. I do believe also that in no other condition is the tinnitus so much influenced by the psychogenic factors of emotion, distress, worry and fatigue. Most of the cases occur after the age of 60. I have observed that in advanced cases of arteriosclerosis with a hyperpiesis a sudden or progressive increase in the tinnitus frequently has a bad prognostic significance and may be the signal of impending calamity.

In all there were 19 cases of tinnitus in which there was no complaint of deafness and no lesion of the conductive or perceptive mechanism could be demonstrated clinically and of these only 12 could be looked upon as of psychogenic origin. The distinction between tinnitus of hysterical origin and that due to organic changes in the acoustic organ, is, as far as I know, almost impossible and it may be that small lesions are the basis on which hysterical complaints are built up as a superstructure. The tinnitus of hysteria, however, is usually of a more complex character and is likened to music, bells or other common sounds. It is my belief that true hysterical tinnitus is an uncommon condition.

I have stated that tinnitus was of almost universal experience, and it is probably true that most people have at one time or another been conscious of tinnitus and for no particular reason. It could be argued that tinnitus is a normal physiological sensation but inaudible and, quite apart from aural disease, there is a body stage that changes the inaudible to the audible and that tinnitus of such origin could be the basis of a hysterical manifestaton. Even were this hypothesis correct the otologist or the psychiatrist would be bold indeed, in the light of our present knowledge, to attribute tinnitus to such an origin without a searching clinical examination. The one diagnostic feature of psychogenic tinnitus is the fact that with appropriate treatment it can usually be cured.

There are other conditions such as intracranial tumours and drug intoxication in which tinnitus can be an important symptom, but not a presenting one. Other conditions, such as malocclusion, I am frankly sceptical about and purposely omit.

With tinnitus there is dysfunction both physical and mental. Only too often a patient will state that he cannot hear on account of the head noises. In such cases this could be looked upon as subjective masking and the degree of loss of hearing as the result of the tinnitus depends upon the intensity and pitch, both of which can be determined audiometrically. In some, and particularly in the degenerative deafness of the elderly, the pitch of the tinnitus is higher than that of the upper limit of the residue of hearing, and little of this subjective masking effect is present and, therefore, a hearing aid can be used with comfort and benefit. Should, however, the pitch of the tinnitus be within the range of the residue of hearing, the masking effect is such that there is an apparent increased loss of hearing and the use of an aid so accentuates the tinnitus as to make the benefit nil and the wearing of it intolerable.

It has been my practice to try to assess the patient's reaction to the tinnitus. Some would readily volunteer the information that they had got accustomed to the head noises; others stated that the noise was only discernible when quiet in the evenings and in bed and should the noise be of the continuous variety they could be unconscious of it when busy or preoccupied. A sifting of the replies to such and similar questions led me to try to determine what I refer to as the distress factor. This was carried out on a points system and of the total number of cases (254), in 209 the distress factor was considered to be mild, in 33 moderate and in 12 severe. In those in which the distress factor was considered to be mild the presence of tinnitus seemed to be of no moment; reassurance was readily accepted and no further advice or help was sought. Where the distress factor was looked upon as moderate I noted that the cases were almost wholly female and the age incidence was around the 41–50 age group. In particular, sleep was disturbed and the effect of masking by external noise and preoccupation was less marked. In those I also thought there was a degree of psychogenic overlay. In only 12 did I consider the distress factor to be severe, and in those there was also a loss of hearing that amounted to a serious disability and which was not compensated for by the use of a hearing aid.

I have no doubt at all that the deafness materially coloured the mental attitude to the tinnitus and also deprived them of that intermittent relief given by background noise. These cases presented a challenge to one's personality and capabilities as a physician. From these figures I conclude that in a very small percentage (4·7) is the mental dysfunction great.

*Prevention of tinnitus.*—With the rapid and total resolution of middle-ear infection, following the use of the antibiotics, neural involvement is less likely. These two factors should in themselves reflect, some years hence, a marked reduction in the incidence of tinnitus, if it is agreed that middle-ear infection is the primary cause in 50% of cases.

As yet, there is no known measure, therapeutic or surgical, that can offer a reasonable hope of alleviation or cure. Thyroxine, Prostigmin, vasoconstrictors and vasodilators I have not found very helpful; the same can be said about the finding and the eradication of septic foci; that therapeutic implement, the eustachian catheter, favoured by many, is likewise in disrepute. It may be that cervical sympathectomy is the answer, but the results of my clinical investigation would not appear to warrant a surgical procedure of such magnitude.

In relating the distress factor to treatment, I am of the opinion that the percentage requiring therapeutic measures is small, and most are content with the assurance that the noise is of little importance and does not signify increasing deafness or impending mental derangement. A few require a mild sedative during readjustment and in my experience this rarely exceeds a period of several weeks. I do feel that greater success is achieved by such an approach and the frank confession that no cure or alleviation can be promised, than an unsuccessful regime of treatment instituted without faith or hope.

SUMMARY

(1) The incidence of tinnitus is related to deafness in a given population and in the various age groups.

(2) Tinnitus is an otological symptom and middle-ear disease is the most common primary ætiological condition.

(3) Cochlear or neural involvement is common to all conditions associated with tinnitus.

(4) Psychogenic tinnitus is uncommon.

(5) Tinnitus gives rise to little distress in the great majority of cases.

(6) There is no known effective treatment.

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**Professor Alexander Kennedy:** *Cochlear, Neural and Subjective Factors in Tinnitus.*—The symptom of tinnitus has in common with many of the symptoms of psychological disorder the fact that it is wholly subjective, and that to assess its nature and severity we are dependent on the patient's description. This is subject to the fallacies inherent in the communication of information from one person to another, including his powers of description, his attitude toward the symptom, the extent to which he pays attention to it, is able to suppress it from his consciousness or is able to interest himself in other matters which focus his attention elsewhere. On the other hand its association with deafness, with demonstrable pathology in the auditory end-organ, with noise-intolerance and with vertigo, indicates that it is a valuable warning of organic disease. None the less, the *factor of preoccupation*, which sustains the patient's attention to his tinnitus, is of considerable importance.

In order to understand the effect of psychological factors on the way tinnitus is described and on the amount of distress it may cause, it will be necessary to draw attention to the factors which influence the patient's account of it. These include:

(1) *His previous auditory experience*, with which the symptom has to be compared, his knowledge of descriptive words for music or sounds, his native intelligence and his inclination for analysing subjective experience.

(2) *The kind of associations which the sound call's up in his mind.* Tinnitus may act as an "unstructured" sound into which the patient may project his own imagination in the same way as he will interpret the ink-blots of the Rorschach test in terms of his interests, or of matters with which he may be occupied. A melancholic patient who said that he could not get "the bells of Hell out of his head" is an example of this.

(3) The extent to which tinnitus is unpleasant and distracting. *The distress factor* will depend not only on the intensity of the sound but on the patient's vulnerability. For instance, several of my own patients who were the subject of endogenous depression, in which there is often a marked diurnal variation in mood, complained that their tinnitus was worse in the mornings. Another patient noticed the symptom when his wife was speaking to him, and hardly at all at other times. Anxious patients notice it when they are trying unsuccessfully to get off to sleep. There is thus some resemblance between the threshold of different patients to pain of moderate severity, and their varying toleration of tinnitus.

The ways in which tinnitus is described are many, but from the point of view of diagnosis, the fact that it is unilateral or bilateral, continuous or intermittent, and whether it varies with posture seem to be most important from the neurological point of view, whereas the localization and kind of sound is a less reliable guide, as it is much more liable to subjective bias. Of the continuous sounds, escaping steam, the sound in a seashell, whistles, bells, taps, streams and ocean beaches, dynamos, radio oscillation and interference noise seem to be the most common. The presence of an intermittent sound is, I think, an indication for careful search for a local lesion and if the patient reaches the psychiatrist first, as he sometimes does, he should be referred for an otological opinion. The extent to which an intermittent sound can be interpreted by the patient is, however, illustrated by the following case:

A man of 46 complained that he had been prevented from getting to sleep by a sound resembling the breaking of waves. He was a rather gloomy man who had little life outside his own home and his doctor gave him tonics and did not at first take the matter very seriously. When, however, he complained that he was the subject of a recurrent nightmare, he at once referred him to a psychiatrist. In the dream he was at a small seaside village where he used to spend his summer holidays as a boy. He could hear the pounding of the waves and the seething of the surf in the pebbles as each wave receded. He would get up and try to walk in his bare feet over the pebbles to get away from the sound but his progress was slow up the steep beach so that it appeared to be overtaking him. He would finally wake up sweating and afraid. The psychiatrist showed some ingenuity in interpreting the dream but was unable to dispel it. Shortly after, waking from his usual nightmare the patient found he could still hear the waves, and woke up his wife and asked her if she could hear them, too. She could. When he next went to the psychiatrist the patient took his wife with him as a witness and the couple were then referred to me as an interesting case of *folie à deux*. On placing my stethoscope on the husband's head I, too, heard the waves and was able to make the diagnosis of angiomatous malformation, which was later confirmed at operation.

One should perhaps say at this point that, from the psychological point of view, there is very considerable doubt as to the validity of tinnitus matching tests except to gain a very general impression. In reproducing a set of sounds and asking the patient to identify the one most resembling his tinnitus (Goodhill, 1952), one is asking a leading question and one may unwittingly be forcing an auditory card on him, as hearing is a sense in which suggestibility can be very marked indeed except in those who have the confidence of the trained musician or concert-goer.

Patients who are referred to a psychiatrist complain of a variety of auditory nuisances but there is rarely any difficulty in distinguishing tinnitus from auditory hallucination. I have several times encountered patients who had tinnitus and auditory hallucinations at the same time and who distinguished between the two without difficulty as if they were of an entirely different *genre*. Although the hallucinated patient will swear that he "hears" the voice of his persecutors, he is concerned with the content of the hallucination and its significance for him and is rather surprised if enquiry is made about his ears and will not admit that this is relevant. Many schizophrenic patients feel that thoughts or messages are put into their head and when they complain that they "hear voices" it is probably because it is the easiest way of explaining how they came to be perceived. Occasionally, however, tinnitus is rationalized as an hallucination as in the case of an elderly man who attributed the annoyance to the activities of the National Assistance Board.

There can be few individuals who have not experienced tinnitus at some time and it seems to be accepted, as minor aches and pains are, as an inevitable experience whenever minor strain is thrown on the auditory apparatus, whether after a blow on the ear, after shooting, after descent in aircraft or in association with a cold. The question arises as to how much of the experience is due to the *cochlear factor* and how much to the *preoccupation factor*. The latter can be illustrated by the analogy of listening to gramophone records. The record and the amplifier have a noise-level of their own but the listener's attention and interest are on the music and the cerebral apparatus is able to discriminate against the noise if it is not above a certain threshold. If, however, the listener is an expert on sound reproduction or has built the apparatus himself in order to eliminate noise, he will pay far more attention to the noise and will not be able to stop adjusting the tone-control, so that the music is spoiled for him. If a patient's attention is once directed to tinnitus and he has little else satisfying to think about, it will continue to distress him. The question also arises as to whether the auditory end-organ may not itself generate a noise-level which has to be eliminated by mechanical damping at the peripheral end and discriminated against in the process of auditory perception. Such a sound might be produced, as tinnitus is, by minor alterations in local conditions or even be present as an accompaniment of normal hearing which is eliminated only above the level of the primary projection areas. The structure of the auditory apparatus is such that it may well either generate endogenous noise or that impulses may add themselves to those which cause the action-potentials in the sensory pathway from the hair-cells. If, in fact, the response of the cochlea is a dual one (Brazier, 1951) consisting of the piezo-electric effect producing the microphonic potential of Wever and Bray (Wever, 1933; Hallpike and Smith, 1937) and the nervous impulses which are sent to the spiral ganglion, minor differences in density of bone and distribution of pressure might well disturb the time-relationship between the two at different frequency levels in the cochlea with consequent alteration of the pattern of neural impulses in the VIII nerve and the production of interference. Failure in the cochlear

damping mechanism or in feed-back circuits with a similar purpose at a higher neural level could have a similar effect. If the method of discrimination at higher levels is, as suggested by Pitts and McCulloch (1947), a scanning mechanism situated in the transverse temporal gyrus with a sweep comparable to that used in television, any electronic analogue which could be made to carry out a similar task would certainly produce a considerable level of noise, especially if the intake had suffered in the process of modulation. In an apparatus so delicate, temporary and minor disturbances can only be expected and the conscious component of nervous activity must ignore them in the way that it normally ignores similar disturbances of vision. Tinnitus at its loudest does not appear to exceed about 15 decibels above threshold in intensity. It may be that in some patients in whom no defect of hearing can be demonstrated the fault lies in failure to eliminate from consciousness, at some point from cochlea to cortex, a sound which the normal subject might be expected to ignore. Distress can, in fact, be caused by tinnitus of no more than 5 decibels in intensity as judged by a comparative test.

### Tinnitus as Seen in a Psychiatric Clinic

Tinnitus is one of about 750 clinical features the presence or absence of which is recorded when a patient is seen in the Durham University Department of Psychological Medicine and I have thus been able to collect the records of those patients in whom it has been present in the last four years and to gain an idea of the kind of patient who complains of it and the features with which it is most often associated. Particular interest attaches to 14 patients whose tinnitus improved as the result of treatment directed solely at underlying psychiatric conditions. On the basis of this rather small material and some previous cases I have attempted a classification of patients who present themselves with tinnitus, from the psychiatric point of view, in order to compare it with groups of cases seen by otologists in whom conditions other than a degree of nerve-deafness have been excluded.

(1) *Depressive preoccupation with tinnitus.*—The commonest psychiatric diagnosis was endogenous depression, a condition in which the patient takes a gloomy view of his circumstances to such an extent that he becomes unhappy and inefficient. The idea of depression is an abstract one and few are content to suffer from an abstraction for long, so that from the first the patient seeks a cause for his mental state. If tinnitus happens to be present, as it often is in the early involutional period when depression is common, the patient becomes preoccupied with it to the exclusion of all else and is thus able to rationalize his depression by telling himself and his doctor that "these noises are spoiling my life and driving me mad". In fact it is the depression which is spoiling his life. There are two main reasons for thinking that this explanation is a reasonable one. Firstly, in discussion with otologists about tinnitus, the question of suicide is often mentioned, indicating that they, too, see depressives with this symptom. Secondly, if the depressive state is treated successfully with electric convulsant therapy, the tinnitus disappears. 11 of my patients were relieved of the symptom in this way.

(2) *Tinnitus as a symptom of psychoneurotic escape.*—In a number of occupations which carry the hazard of deafness, the workers experience tinnitus, especially before they become accustomed to the noise. In the course of artillery training, tinnitus must be universal and the extent to which the recruit is prepared to ignore it is determined as much by his enthusiasm for the weapon and his morale generally, as by otological considerations. The patient who cannot understand his job or is afraid of it, is less likely to accomplish the psychological part of the normal process of suppression of the sound and is more likely to welcome the symptom as suitable to his unconscious purpose of evasion of the unpleasant without loss of self-respect. The choice of symptom on which he bases his functional incapacity is here made for him by the presence of a disability which is accepted as a normal hazard. There were two civilian patients who illustrated this mental mechanism.

(3) *Anxiety states—psychosomatic tinnitus.*—In a study of human reactions to danger I have shown that different individuals according to their constitution feel anxiety before dangerous events in different ways, just as before an examination or a race some experience frequency of micturition, some have epigastric sensations, others palpitation, yet others vertigo. One of the less common groups is that which experiences a feeling of unreality coupled with singing sounds in the ears. When, in such a person, there is persisting anxiety due to unsolved personal problems or frustration of ambition, it is felt in the vulnerable system and instead of the much commoner gastric or cardiac neurosis, tinnitus may be the most prominent symptom. One patient was successfuly treated on this basis.

(4) *Presenile, senile and arteriopathic deterioration.*—The most surprising finding on examining the material was the number of cases of the rarer presenile dementias in which this symptom was experienced in the early stages of the disease. While some of these patients were hypertensive the majority were not. The pattern of cerebral disorder varied from cortical atrophy and diffuse sclerosis to more generalized disorders of the Alzheimer type. None of the patients had major thromboses. As deterioration advanced, tinnitus ceased to cause distress.

(5) *Malignant hypochondriasis.*—Rhinologists as well as dental and plastic surgeons will be familiar with the relatively uncommon but well-remembered patient who is preoccupied with a minor deformity of the nose or lips or with symptoms thought to originate in sinus infection, who insists he has never had the right treatment and that surgery will make the whole difference to his life. This

condition, to which I have given the name malignant hypochondriasis (1950, 1953) often overlies a gradual and serious deterioration of the personality and it is most unwise to operate for what is, in fact, a delusion, even though some justification can be found in the presence of actual anomalies. When tinnitus is the symptom upon which the patient has fixed, operating at his insistence and against one's better judgment is a sure way of joining the list of medical men whom the patient considers have helped him on the downward path.

There is no doubt that tinnitus is a symptom indicative of organic disease which can cause real distress. The distress factor is, however, related to the extent of the patient's preoccupation with the symptom and his attitude of mind towards it. It is impossible to consider the tinnitus without the patient. Before operative treatment is contemplated, such as section of the chorda tympani, destruction of Jacobson's plexus or of the labyrinth, or even section of the VIII nerve, some attempt should be made to explore the possibility of raising the threshold at which the symptom interferes with the patient's life. The use of sedatives is, of course, as much upon the patient as upon the tinnitus, and phenobarbitone may for a while erect a screen between him and his symptom. Unsuccessful operation will leave him still more preoccupied with aural function. The results with the depressive group alone would suggest that if psychiatric help is to be sought, it should be sought early to avoid needless suffering.

Finally, there is little doubt that even section of the VIII nerve may not remove tinnitus. It is capable of becoming fixed centrally in the same manner as the phantom pain in an amputated limb or the pain of causalgia. In some patients with fixed central pain, operations of the leucotomy or cortical topectomy type are remarkably successful at a variable cost to the patient's general efficiency and adaptation to life. I have had no experience with such an operation for persistent tinnitus but on theoretical grounds it might be justifiable if it seemed that the patient's life was otherwise not worth living.

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**Dr. Alick Elithorn** (Member of the Neurological Research Unit of the Medical Research Council, National Hospital, Queen Square, W.C.1): *Prefrontal Leucotomy in the Treatment of Tinnitus.*—It was quite clear that most patients were able to adapt themselves to a persisting tinnitus. There were, however, a few who did not and he was in agreement with Professor Kennedy's classification of the psychiatric background of these patients. He wished to report briefly on 17 patients, all complaining of tinnitus, who had come to leucotomy because other treatments (both physical and psychological) had failed to produce appreciable relief. These patients had all been under the care of Dr. Eliot Slater, and he would like to express his gratitude for Dr. Slater's kindness in giving him access to his material and for encouraging him to make this analysis. All but 3 of the patients were seen personally, both before and after the operation.

These patients fell into three main groups. First, there were those whose illness was primarily psychiatric and in whom the tinnitus was only the focal point of their subjective distress. 3 patients were in this group. All 3 suffered from depressive illnesses of the involutional type. 2 had been subject to and had tolerated their tinnitus for many years before the onset of their depressive illnesses. Treatment here was that of the psychiatric disorder and these patients had come to leucotomy either because of failure to respond to E.C.T. or because this was contra-indicated.

In the remaining 14 patients, the tinnitus was the presumptive cause of illness. This group could rather arbitrarily be divided into two: First there were those patients who had either a definite history of a previous psychiatric breakdown, or a personality of the psychoneurotic type, and whose tinnitus precipitated an illness with very definite psychiatric features. Second, there were those who, until their present illness, had shown little evidence of psychiatric instability but who found the stress of a continuous tinnitus more than they could tolerate. This division was advisedly described as arbitrary and in fact it proved easier to rank this small group of patients in order of stability of personality than to divide them into normal and abnormal.

In discussing these patients with the speaker, Mr. Cawthorne had said that he had found that, in addition to those patients whose intolerance of tinnitus was primarily psychiatric, there was also a small group of women of good personality and generally over 55 years of age who reacted badly to a tinnitus and failed to accept it as an unimportant symptom. In the present series, 7 of the patients were male; on inspecting the personality ratings it was found that the first 9 had had no previous history of definite nervous trouble. Of these only 2 were men, both of whom had had severe organic

cerebral changes. Thus this small series confirmed that, in the absence of a history of nervous instability, women find tinnitus a more intolerable symptom than do men.

With regard to results, these were very encouraging. Although no patient had completely lost his tinnitus, 9 subjects had made a really worth-while degree of improvement which had lasted at least six months without any sign of relapse at the time of follow-up. 4 of these 9 had been operated on over two years ago. Of the remaining 8 patients, 4 showed varying degrees of improvement, 3 were essentially unchanged and 1, a man with severe organic cerebral damage following meningitis, became worse.

With regard to the quality of the improvement: no patient became free from tinnitus, many still maintained that the noises were as bad as ever, yet in some way every patient was able to adjust better to his noises. This appeared mainly as an improvement in mood and as a reduction in the amount of attention paid to the tinnitus which had become, as it were, shifted towards the periphery of consciousness. Because of this persistence of their main symptom, some patients were loth to admit improvement which their relatives clearly noted. The following is an example of a worth-while operation, whose value was reluctantly admitted by the patient:

A woman of 62, described by her husband as previously active, busy, jolly and of a happy disposition, and whose history gave no evidence of previous nervous trouble, developed four years before admission a severe tinnitus. Examination revealed a mild bilateral nerve deafness. She became increasingly agitated and depressed, lost all interest and energy and barely managed to cope with her immediate household affairs. Fifteen months after a modified leucotomy she replied when asked about her symptoms: "I still have the noise—plenty of it—especially at night. It upsets me dreadfully." Her husband's reply was quite different: "A great improvement, she's more like a human being . . . Now she's got many outside interests and only complains of the noises at night." In brief, the patient still has her tinnitus but it is now no longer her main occupation nor is it a cause of continuous distress. Both the patient and her husband denied the presence of any post-operative defects but it is probable that her energy output had been slightly decreased, though still very normal for her age.

In every case a very careful attempt was made to detect post-operative personality defects, and the opinion of a relative was sought in all 17 cases. In addition to the man who was worse, 2 patients showed definite frontal syndromes. These were not severe enough to make the operation a failure. 7 other patients showed minor changes in personality in that they were at times outspoken or tactless or that they were less affectionate or showed some diminution in drive and energy. None of these defects were, however, sufficient to prevent the patient's return to normal social life. In the remaining 7 patients it was not possible to detect any definite change in personality and such changes were denied by their relatives. This small amount of post-operative personality impairment was largely due to the fact that only 3 patients had had a classical leucotomy. These were, in fact, the 3 patients who showed marked personality changes. The remaining patients had had modified operations. These modified operations had been designed by Mr. Harvey Jackson and Mr. Wylie McKissock, who have described their respective techniques elsewhere.

It was not claimed that many patients suffering from tinnitus need even a modified leucotomy, but there was undoubtedly a very small group in whom the operation should be considered. The main indications were: first, that the patient must suffer genuine distress: in establishing this the routine interview of a relative by a psychiatric social worker was of great assistance. A home visit might disclose that once outside the consulting room the patient evidenced few objective signs of suffering. Second, there should be a sound personality and evidence of some attempt to deal with the disability. Finally, there should have been a determined effort to treat the patient with less radical methods.

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**Mr. T. E. Cawthorne** said that he had seen a large number of patients who had tinnitus which did not seem to worry them. It was only in a relatively small proportion that it gave rise to those troubles of which they had heard and the patients nearly always had something else wrong with them.

Of a large series of cases of otosclerosis numbering 1,150, which he had investigated, he had found that 87% had tinnitus, but of these only a very small proportion, less than 10%, found the tinnitus troublesome. In such cases an explanation was usually to be found in their temperament, as all those who were troubled by tinnitus were of a nervous temperament. In Ménière's disease tinnitus could sometimes be a very useful thing in that it revealed which side was affected in a patient who had deafness in both ears and who got attacks of giddiness. There was another series of cases of which he thought they had seen quite a number, where patients had infective disease in one ear and had attacks of giddiness as well. If one went into these cases carefully it might be found that the attacks of giddiness came on with tinnitus and deafness in the sound ear.

Perhaps the most depressing series of cases they saw were in those people who had had a previous operation to try to cure the tinnitus. Where the tinnitus was the primary complaint he had never seen

any patient helped by any form of operation on the labyrinth or VIII nerve. It was a truism that if anybody had tinnitus and had an operation (here he was leaving out the question of leucotomy, and was thinking of operations on the labyrinth or VIII nerve) to improve it, and it did not disappear, the patient would be made worse.

He had in the distant past carried out various operations on patients for tinnitus and he had seen from time to time patients who had been submitted to operations done by other surgeons and still had tinnitus, and were really the despair of the otologist. More recently Dr. Eliot Slater at the National Hospital, Queen Square, whom Dr. Elithorn represented, had been able to help a small number of patients by recommending prefrontal leucotomy. This had been carried out by Mr. McKissock and they had heard from Dr. Elithorn of the results. It was a great comfort to know that at least something could be done for a small number of these cases.

**Mr. E. D. D. Davis** desired to take the opportunity of paying a tribute to the work of the late E. Garnett Passe. Three or four years ago Garnett Passe initiated an experimental investigation of the control of the sympathetic nervous system on the vascular mechanism of the ear and its effect on tinnitus and vertigo. With the help of Mr. C. P. Wilson and Mr. J. P. Monkhouse of the Ferens Institute, Dr. J. C. Seymour carried out these experiments on animals. No doubt Dr. Seymour would publish these results later. Albert A. Gray in 1926 advanced the theory that tinnitus was a vascular disturbance within the cochlea. The dilatation and constriction of the capillaries of the canal of the cochlea would probably produce variations in the pressure of the endolymph. The theory that tinnitus was caused by stimulation of the auditory nerve was excluded by Dandy's operation for division of the nerve and destruction of the modiolus of the cochlea by others. Tinnitus persisted after these operations. Garnett Passe considered that tinnitus and vertigo were caused by a neurovascular disturbance. He injected procaine into the stellate ganglion and found that the tinnitus and vertigo disappeared temporarily and Horner's syndrome was present. Later he removed the stellate ganglion and stripped the vertebral artery of its sympathetic fibres. Later still he excised the sympathetic ganglia connected to the II and III dorsal spinal nerves. The tinnitus of otosclerosis was not relieved by cervical or dorsal sympathectomy. He performed stellectomy in 30 cases: 5 were completely relieved; reduction of symptoms in 10 cases and no benefit in 15. By relief he meant that the patient no longer complained of tinnitus after stellectomy. *Dorsal sympathectomy*, 40 cases: complete relief in 6 cases; reduction of symptoms in 21; no benefit in 9; no reply from 4.

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# Section of Urology

President—J. G. YATES-BELL, M.B., F.R.C.S.

[*February* 26, 1953]

## DISCUSSION ON MALE INFERTILITY

**Dr. G. I. M. Swyer:** Since the husband is considered to be wholly or partly to blame for more than 50% of infertile marriages, it is clear that in the past the wife has received more than her fair share of attention at the expense of the husband. With increasing attention being paid to the male factor, knowledge of male gonadal function is slowly growing. Nevertheless it is still fair to say that we have little idea of the cause of, or the remedy for, defective spermatogenesis in most cases.

There are one or two practical aspects of the ætiological problem which should be better known. For example, a testicle which is not inside the scrotum *at the time when spermatogenesis ought to begin* will never produce spermatozoa, even if it be brought into the scrotum later. So that boys with undescended testicles should not be allowed to go on to puberty in the hope that spontaneous descent may occur; if it does not, the inevitable result is sterility. And again: it is very easy to leave the testicular blood supply impaired after operations for the cure of inguinal hernia, and surgeons in general should be more aware of the sterility that not uncommonly results from the slow degenerative changes in the testis following such vascular obstruction.

Diagnosis and prognosis can be considered together since they are concerned with the decision as to whether a man is fertile, or, if not, just how much of a chance he stands of producing a pregnancy at all. The history and the findings on physical examination are usually not illuminating, but since they sometimes give the key to the individual problem, they should seldom be omitted. The key test, of course, is the seminal analysis.

### SEMINAL ANALYSIS

The exact length of the period of continence which should precede the production of seminal fluid for analysis is probably not very critical. Farris (1950) adduces evidence that a five-day period of continence has advantages over a shorter period but my own observations do not altogether support this view. He believes that some men require five days to reach their optimal sperm densities, though others may reach them in three days. On the other hand, since an average coital frequency is of the order of twice a week, it can be argued that the seminal fluid, as tested after a three-day period of continence, will give the better picture of conditions in actual practice. An indefinitely prolonged period of continence is merely misleading, since, though it may increase the sperm density, it will also greatly increase the abnormal morphology and proportion of immotile or feebly motile spermatozoa.

Doubts of no kind may be permitted regarding the best way of producing the seminal specimen. It is still not universally appreciated that condom specimens contain no moving spermatozoa; and patients have had costly courses of injections because their spermatozoa, produced in a condom, showed no activity. Coitus interruptus will seldom permit collection of the entire specimen; and since the ejaculated semen is far from homogeneous, the sources of error introduced by this technique have often led to the wildest mistakes. Scooping the semen from the vagina after intercourse—even this has been advocated—is still more unreliable. Distasteful as it may be to some doctors to recommend it and to some men to perform it, the conclusion is inescapable that masturbation is the only worthwhile technique for collecting seminal fluid for analysis.

The clean, dry glass jar as a receptacle is appreciated by all of us; but how many are aware, as are the cattle artificial insemination workers, of the profound susceptibility of spermatozoa to temperature shock? Strictly, the glass jar should be at about 30° C. before the semen touches it, and it should be cooled slowly to room temperature. In cold weather it is wise to instruct the patient to warm the jar, perhaps by keeping it in an inside pocket for ten minutes, before collecting the seminal fluid.

The volume of semen matters only when it is either small—for then little if any interface may exist between ejaculate and cervical mucus—or unduly large, for then a normal total number of spermatozoa may be so diluted down that few have an opportunity of reaching the cervical canal.

The sperm density is usually looked upon as the most important single criterion in determining the adequacy or otherwise of semen. The tendency nowadays, based on increasingly reliable data, is to consider the lower limit of density to be a good deal less than was formerly thought. MacLeod (1951), for example, whose comparisons of the findings in 1,000 fertile men and in 1,000 husbands of infertile marriages are outstanding, considers 20 millions per ml. to be the dividing line. Above this figure excellence of activity and smallness of the proportion of abnormal forms are more important in the determination of likelihood to fertilize, while below this figure these other criteria were of little consequence. My own small series suggests a comparable influence of density upon likelihood to fertilize.

The sperm densities of seminal samples from 90 men whose wives conceived have been arranged in the following groups: less than 20 millions per ml.; 20–50 millions per ml.; 50–100 millions per ml.; and more than 100 millions per ml. These 90 men came from a group of 456 men attending the Fertility Clinic and providing seminal specimens for analysis, the results of which have been arranged in similar groups. If the likelihood to fertilize were independent of sperm density, it would be expected that the proportion of men producing pregnancies in each group would be about the same; while if greater density meant greater likelihood to fertilize, then the proportion of men producing pregnancies would increase as the sperm density increased. As can be seen (Figs. 1, 2) the latter holds

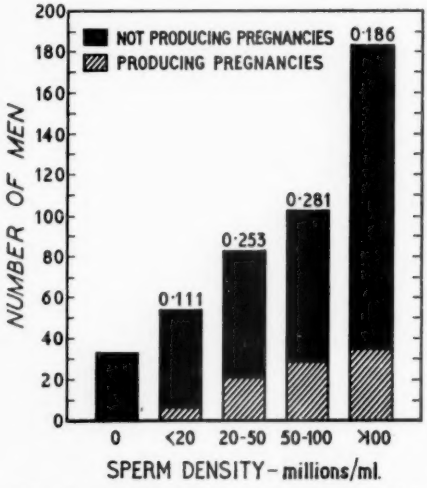


FIG. 1.—The distribution of sperm densities in seminal specimens provided by 456 men attending a fertility clinic, and of the densities of specimens provided by 90 of these men whose wives conceived.

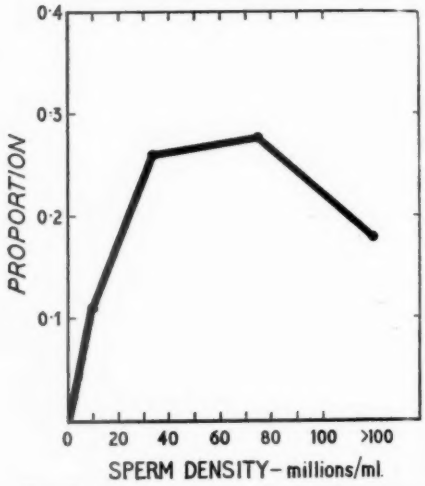


FIG. 2.—The proportions of seminal specimens from men producing pregnancies to the total number of specimens in each sperm density group, plotted in relation to sperm density.

true up to a point only, since the proportion of men producing pregnancies in the group with highest sperm density is lower than in the two preceding groups. These findings suggest that the acceptable lower limit for sperm density, other features of the semen being satisfactory, lies between 20 and 50 millions per ml. and I am inclined to place it at about the 30 million mark.

Since only moving spermatozoa can have a chance of fertilizing the ovum, Farris (1950) has proposed that the total number of moving spermatozoa is the best guide to the fertilizing potentialities of seminal fluid. He uses three grades: (1) Fully fertile, with more than 180 million total moving spermatozoa; (2) relatively fertile, with 80–180 million and (3) subfertile, with less than 80 million total moving spermatozoa in the ejaculate. This is an attempt to put the matter on a more precise basis than that usually followed, so it is only fair to point out that there may be inherent fallacies. To determine the total number of moving spermatozoa, the semen is diluted with a suitable diluent and a count of the moving spermatozoa is made in a hæmocytometer chamber. In general, the number of moving spermatozoa in the diluted fluid will be less than that in the original semen, and if no regard is paid to temperature changes, it may be very much less. The susceptibility of the spermatozoa to the deleterious action of the diluent will, of course, vary from semen to semen, so that an unpredictable variation is introduced by this technique, the precision of which is thus more apparent than real.

There seems little doubt that none of the commonly used methods for estimating the activity of the spermatozoa is satisfactory. Counts of the proportion of moving spermatozoa have little value unless a further estimate is made of the speed of travel of the spermatozoa, as well as of the proportion showing translational, as opposed to merely vibrational, activity. I have myself used a semi-subjective method, originally devised by Emmens (1947) and shown by him to have statistical validity, in which a score from 0–4 is given according to the vigour of spermatozoal activity, the approximate proportion of moving sperms, and the approximate proportion of those showing translational to those showing vibrational motion. Though far from perfect, this seems to be fairly satisfactory in practice. No doubt the future will see the development of a purely physical method for estimating sperm activity. This has been achieved (impedance change frequency) for cattle but is not yet applicable to humans.

Abnormal spermatozoal morphology has received considerable—and probably unwarranted—attention in the past. I shall merely comment on a fairly widely held view that increased proportions of abnormal forms carry an increased risk of abortion, should conception occur.

I know of no evidence to support this view, while MacLeod's (1951) data are against it, and so are those of Bender (1952). I have collected some figures from my own records and can compare the seminal findings in 58 specimens provided by 28 men whose wives conceived but aborted with those in 100 specimens provided by 63 other men whose wives conceived and went to term (Table I). It

TABLE I.—MEAN VALUES AND STANDARD DEVIATIONS FOR VOLUME, DENSITY, ACTIVITY AND MORPHOLOGY IN THREE GROUPS OF FERTILE MEN, SHOWING NEGATIVE CORRELATION WITH ABORTION

| Group | Volume (ml.) | Density (millions/ml.) | 5-hour motility* | Abnormal forms (%) |
|---|---|---|---|---|
| 63 men whose wives conceived and went to term .. .. .. | 3·59 ± 1·90 (100) | 92·82 ± 94·02 (100) | 52·0 ± 31·25 (94) | 33·74 ± 11·89 (99) |
| 28 men whose wives conceived but aborted .. .. .. .. | 3·46 ± 1·64 (58) | 70·3 ± 74·1 (57) | 52·34 ± 32·65 (55) | 32·46 ± 16·07 (52) |
| 22 men whose wives had had 3 or more consecutive abortions .. | 3·69 ± 1·79 (22) | 131·0 ± 76·20 (22) | 73·20 ± 24·97 (22) | 25·9 ± 9·29 (22) |

*This is the interpolated motility score at 5 hours, expressed as a percentage of the maximum.

is perfectly obvious that there is nothing whatever to choose between the two groups. A further, and still more selected, group consisted of 22 men whose wives had had 3 or more abortions. If there were anything in the hypothesis, the seminal analyses from these men should show a clear excess of abnormal forms. On the contrary, the mean figures for this group are the best of all; and since the variances are less than for the other groups, it implies that these men formed a more homogeneous group in respect of seminal excellence than did those of the others.

I must emphasize, even though only in passing, the great variability from specimen to specimen commonly encountered in seminal analysis. The important conclusion to be drawn is that a single poor result may mean nothing; it merely indicates the need for at least two further specimens to confirm or refute the original findings. It is always wise, before reaching a final conclusion, to do a post-coital test, since this may prove entirely adequate even though repeated seminal specimens fail to measure up to the desired standards. Particularly is this discrepancy likely to occur when spermatozoal motility is the faulty factor in the seminal analysis.

## OTHER SPECIAL TESTS

Other studies of the male which have a place in the investigation of infertility are: testicular biopsy; basal metabolic rate determination; estimation of F.S.H. (follicle stimulating hormone) excretion; and estimation of 17-ketosteroid excretion. Testicular biopsy will be dealt with by Mr. Tulloch. The second is not much used in this country, though it is commonly employed in the United States where there is a widespread belief that if the B.M.R. is below normal, spermatogenesis may be defective; and it is further thought that subclinical hypometabolism may occur, detectable only by measuring the B.M.R. Very little evidence for either of these views has been adduced.

Estimation of F.S.H. excretion is of great value in cases of hypogonadism, for it shows whether the fault lies primarily in the testes (in which case the F.S.H. output will be high, the pituitary being overactive) or in the anterior lobe of the pituitary gland (when the F.S.H. output is low or zero). When hypogonadism is of testicular origin, it is perfectly clear that no form of treatment can induce spermatogenesis, since there is already an excess of the normal stimulating hormone. In particular, the hope of producing any effects from further stimulation with gonadotrophic hormones is obviously forlorn.

Estimation of 17-ketosteroids gives a rough measure of the secretion of male hormone by the interstitial cells of the testis. It will be remembered that a proportion of the 17-ketosteroids arises from the adrenal cortex in both men and women; therefore, if no androgens are being produced by the testis, the 17-ketosteroid output will be similar to that of women, and since this, even on the average, is not very different from that of men, the interpretation of this investigation may be difficult. More information can be obtained from a clinical appraisal of the man—the extent and distribution of facial and bodily hair; the pitch of the voice; the extent of his muscular development and bodily proportions; and the size of his penis and scrotum—than from the estimation of his 17-ketosteroid output.

It will thus be appreciated that the value of these special investigations of the male is strictly limited.

## TREATMENT

I know of no therapy which can be expected to give good results in cases of oligospermia. When oligospermia is due to obstruction in the epididymis, be it the result of gonococcal epididymo-orchitis, microcyst of the epididymis or other obscure lesion, vaso-epididymostomy offers at least a theoretical

chance of success. I think the prevalent view in this country, propagated mainly by surgeons who have had little experience of the technique, is unduly pessimistic. Bayle (1952) of Paris, who has probably done more of these operations than anyone else, has obtained something like 66% of success in patients who, on exploration, proved amenable to such surgery. He feels that since the operation can do no harm and may do much good, there is a great deal to be said in favour of it. To succeed, however, apart from the requirements of active spermatogenesis, free passage of spermatozoa into the head of the epididymis and patency of the vas deferens and ejaculatory ducts, the operation must be performed with great delicacy, as in an eye operation, and tuberculosis must not be the ætiological factor.

The other cause of azoospermia which may be amenable to treatment is secondary hypogonadism, where the testes are themselves normal but have never received adequate gonadotrophic stimulation. In such eunuchoids prolonged testosterone therapy by implantation, in addition to bringing about the expected general somatic changes, may eventually lead to normal testicular spermatogenetic function and full fertility (Swyer, 1951). Similar results have also been reported by Hurxthal *et al.* (1949).

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**Mr. W. Selby Tulloch:** *Testicular biopsy: Indications and technique.*—I propose to discuss briefly the indications for a biopsy from the testis and the simple technique of this procedure.

Direct evidence of the state of spermatogenesis may be obtained from the biopsy tissue, and pathological disturbance of the seminiferous tubules may be easily recognized. Biopsy is a valuable diagnostic procedure in investigating the subfertile male. The indications for its use are:

(*a*) In azoospermia, to distinguish between obstructive and non-obstructive lesions.
(*b*) In low seminal counts, to differentiate between arrested spermatogenesis and post-inflammatory states.
(*c*) In any specific cases, to assist with the prognosis and to determine the severity of the process and the capacity of the tubules to regenerate.
(*d*) In assessing the effects of various therapeutic agents, by direct examination to determine the efficacy of specific therapy.

The common causes of testicular changes are divided into two main groups: congenital and acquired.

*Congenital causes.*—Testicular hypoplasia, cryptorchidism, congenital abnormalities, such as the absence of the vas deferens or failure of complete formation of the lumen from the testes to the ejaculatory ducts, and endocrine disturbances causing failure of maturation of the germinal epithelium.

*Acquired causes.*—These include inflammatory states, such as gonorrhœal infection, non-specific urethritis (both these conditions may gradually disappear as a cause, because of the remarkable effects of chemotherapy and antibiotics); tuberculous epididymitis is a common cause, and, rarely nowadays, syphilis; traumatic injury of the testes, mumps orchitis, and irradiation with deep X-ray therapy. With the more extensive use of irradiation, particularly in ankylosing spondylitis, which occurs commonly in the young adult male, although attempts may be made to protect the testes, there is often gross destruction of the germinal epithelium. Even if conception does take place there may be an effect on fœtal development. In the treatment of malignant tumours of the testicle, an attempt should also be made to protect the remaining testicle. Another cause of acquired change in the testicle is the therapeutic use of œstrogens in the male.

As long ago as 1913 Huhner described his procedure of testicular puncture. The investigation was carried out in all his cases of azoospermia in an endeavour to differentiate between obstructive and non-obstructive lesions, i.e. if spermatozoa were found then the lesion was presumed obstructive. However, it is obvious that this procedure has its limitations, because a positive finding would be significant, whereas a negative finding would mean nothing. The technique adopted by Huhner was, without anæsthesia, to use a large bore needle which was plunged through the entire length of the epididymis and testicle, and, on withdrawal, suction was applied throughout. The material withdrawn was immediately examined for spermatozoa. Although I have no personal experience with this method of investigation, it seems to be a rather unpleasant procedure.

For careful direct microscopic study of the seminiferous tubules it is necessary to adopt the procedure of testicular biopsy, which was first carried out by Hotchkiss in the U.S.A. This consists of the excision of a small portion of the testicle, so small that its removal has no effect on the gland, but large enough to include a representative group of the tubules. It has been suggested that this method may not produce a representative portion of the testis. However, some observers who have cut serial sections through the whole testis have shown that the general pattern is consistent.

*Technique.*—This operation is extremely simple and it is done in the Out-Patient Department under local anæsthesia. Each operator will quickly develop his own method, but I shall describe mine. After the area has been carefully cleansed, the spermatic cord is held between thumb and forefinger. About 5 c.c. of local anæsthetic (10% procaine) are injected, and if the injection is in the correct tissue plane the cord is felt to distend. This concentration of local anæsthetic acts almost immediately, and by simple squeezing of the testicle it can be determined whether or not testicular sensation is lost. This is a very definite and certain test for the success of anæsthesia. The scrotal skin over the convex surface of the testis is then stretched and about 1 c.c. of local anæsthetic is injected. An incision is made through the layers of the scrotum. The tunica albuginea is incised 1 cm. or less, and by pressure on the testicle a small portion of seminiferous tubules prolapse. A piece approximately 5 mm. in diameter is removed. The tunica albuginea is approximated with a fine catgut suture. The skin is closed with silk. Immediate fixation is necessary, preferably with a fixative such as Bouin's fluid containing 1% urea, which coagulates the tissue. It is unusual for patients undergoing this procedure to lose any time from work. There are virtually no complications from this operation.

[Lantern slides were shown of representative sections of the various forms of pathology revealed by testicular biopsy.]

*Conclusions.*—By the use of biopsies it can be decided whether or not the case may respond to treatment. Obviously if the biopsy shows complete destruction of the germinal cell layer, treatment is of no avail. In such cases the position can be made quite clear to the patient, a state of indecision and futile hope avoided, and advice given regarding adoption. In cases showing underdevelopment or partial destruction of the essential cells, repeated biopsies may well determine the efficacy of any treatment instituted. It is possible that in future a biopsy may be considered of more value than the detailed sperm count, especially in that wide group of cases where the cell count is depressed below the normal level.

**Mr. Reynold H. Boyd:** There is rightly much pessimism and scepticism regarding the medicinal or hormonal treatment of oligozoospermia. Nothing can improve a *Fixed Low Count* due to partial testicular atrophy, which, if necessary, can be proven by biopsy. Such a fixed low count must be accepted and the best use made of it by

(1) Concentrating intercourse around the time of ovulation.
(2) Artificial insemination using the whole ejaculate by the plastic cap and crooked cannula technique (Fig. 1).
(3) Artificial insemination after centrifuging and adding hyalased-fructose solution.

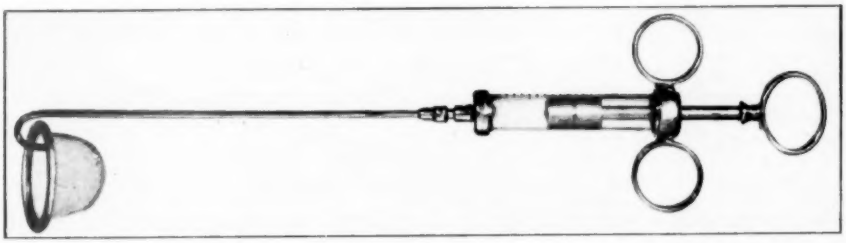

FIG. 1.—Plastic cap and crooked introducing cannula for A.I. in cases of gross oligozoospermia. The cap is inserted and pressed on the cervix, where it is held by bullet forceps while the whole ejaculate of semen is introduced through the crooked cannula.

I do not, however, believe that the *Fluctuating Low Count* is hopeless just because our present gonadotrophins prove capricious or unsatisfactory. The fact that these counts are variable—and I am speaking in terms of fives or tens of millions—shows that spermatogenesis is being depressed or stimulated by some cause. Hope in this field lies in

(*a*) Active pituitary extracts.
(*b*) Irradiation of the pituitary.

The dosage I am at present using is:

Two treatments of 80 r of pituitary irradiation, one week apart, first by exposure on the left side and then by exposure on the right side, totalling 160 air r, corresponding to a tissue dose of about 80 r in the pituitary area. The other factors are 200 kVp; 15 mA; H.V.L. 1·1 mm. Cu; 1·0 mm. Al + 0·5 mm. Cu added filter; 50 cm. S.T.D. and a 7 cm. diameter portal.

Pre-requisite: There must be spermatogenic tissue to stimulate.

There is considerable overlap in the commonest causes of oligozoospermia and azoospermia. Analysis of 500 of my own cases has shown these causes to be:

(1) *Bilateral Gonococcal Epididymitis* which is, year by year, becoming rarer. In the last 200 cases of gonococcal urethritis at three Essex V.D. Clinics there was not one case, although there were two

with unilateral epididymitis. In my experience this is the most satisfactory condition for vaso-epididymostomy, which may be successfully performed five, ten, or fifteen years later. In some cases, when there has been extensive epididymo-orchitis, the upper pole of the epididymis and the rete testis are, however, affected beyond anastomotic help;

and *Bilateral Recurrent Non-specific Epididymitis.* This was 1% in my series. It is much less hopeful and operation here reveals hard, grating fibrosis and no bulging or sperm-containing tubules. The use of antibiotics or sulphonamides in genito-urinary infection has also greatly lessened the incidence of this form of epididymitis, and I believe that in the future early combined use of cortisone or ACTH and antibiotics may break down recently formed granulation tissue and prevent subsequent sterility.

The whole success of vaso-epididymostomy depends not only on meticulous technique but also on careful selection by:

(*a*) Providing normal spermatogenesis by biopsy. The rete testis area and head of epididymis can be palpated at the same time by inserting the little finger.

(*b*) Excluding absence of the vas.

(*c*) Excluding tuberculous infection of vas or epididymis.

(2) Among the more unusual causes in my series were:

(i) *Idiopathic Absence of Ejaculation* and *Absence of Ejaculation* due to lumbo-dorsal sympathectomy for malignant hypertension.

(ii) Complications following *Operations for Slipped Lumbar Disk*—actually partial paraplegia due to damage of nerve roots.

(iii) *Retrograde ejaculation of neurogenic origin.*

All these are suitable cases for A.I. (though in hypertension it may not be desirable). The expressed semen in retrograde ejaculation must be collected by means of a Guyon catheter prior to insemination by intra-uterine or intra-cervical method.

Leaving the rarer causes we come to four main groups.

(3) *Testicular under-development and atrophy* of uncertain origin account for 35% of my cases of azoospermia.

(4) *Bilateral cryptorchism* which accounts for a further 15% of azoospermia. There is urgent need for an analysis of operation results and too few cases are followed up. My own feeling is that there is still room for improvement in operation results and indeed of the whole management of undescended testes.

(5) *Varicocele* is, I think, a frequent cause of moderate oligozoospermia and, at times, of grossly low counts. Here there is room for improvement in our approach and treatment—operation in my own hands not always proving beneficial.

(6) And lastly *Mumps orchitis.* Seguy in his analysis of 2,000 cases of azoospermia gave this to be the cause in 11% and in my own series it is the cause of a like percentage and also of many cases of gross oligozoospermia amounting to actual sterility. On the other hand, Werner (1950) has stated that only 1·7% of adults with mumps get orchitis and of those only 15% are impaired. Clinic figures here seem to refute this statement. Surely this is another preventable cause of infertility.

The infection is brought to the testicle by the blood stream and results in two types of orchitis.

(*a*) The classical fulminant type: The exudative inflammation seems to soften and destroy the membrana propria and to force a way into the seminal ducts after which it spreads ever more widely, destroying within a few days the greater part of the spermatogenic tissue though here and there are islets which may remain unaffected.

(*b*) The quiescent type: This is even more destructive than the fulminant type.

Atrophy ensues at times within the space of three to four weeks but usually within two months. Local changes assessed by palpation are by no means always accurate and can be gravely over-optimistic. Mild unilateral cases recover fertility but bilateral are of grave significance. Prevention of this complication has been tried by giving convalescent serum but large doses are necessary and the method is usually not practical. Latterly the employment of *stilbœstrol* to reduce spermatogenic activity *plus antibiotics* has offered hope as a preventive measure and it would seem that cortisone or ACTH should also be used at the earliest moment in the actual treatment.

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**Mr. William S. Mack** said that he had recently reviewed a series of cases of infertility over a period of eight years. He proposed to deal with one aspect, namely, infertility associated with undescended testicles. The total number of patients investigated for male infertility during the eight-year period was 2,433, of whom 1,096 showed some degree of subfertility. There were 108 patients with undescended testicles. 11 with unilateral descent lay in the normal range of fertility and 97 were subfertile. He had divided them as follows:

| | | Seminal fluid | | | |
|---|---|---|---|---|---|
| | | Normal | Impaired | Grossly impaired | Sperm absent |
| Unilateral, no operation .. .. | 37 | 7 | 8 | 12 | 10 |
| Unilateral, with operation .. .. | 23 | 4 | 11 | 4 | 4 |
| Bilateral, no operation .. .. | 21 | 0 | 0 | 5 | 16 |
| Bilateral, with operation .. .. | 27 | 0 | 2 | 3 | 22 |
| | | 11 | 21 | 24 | 52 |

These patients had been treated by a number of different surgeons and physicians and it was obvious that there was very little agreement about the correct line of treatment since many patients had been left without treatment and others had been operated on at various ages, the operation consisting either of removal of the testicle, or attempts to bring it down. As expected, where no operation had been carried out in bilateral undescended testicles, most patients showed a total absence of sperms, though in a very few cases a few sperms were present. Operation in bilateral cases improved the prospects a little but not greatly. The unilateral descents, with or without operation, were most interesting. Even when the descended testicle felt normal many of the patients showed either complete sterility or gross impairment and biopsy of some of these apparently healthy testicles did show that their development was incomplete. At first sight the prognosis as regards fertility in undescended testicles looked gloomy in the extreme if one was to judge by these results alone.

However, on reviewing a series of cases referred to him for operation, because of maldescent of the testicles, he had been struck by the fact that the majority of these patients were not suffering from failure of descent at all but from ectopia into the superficial inguinal pouch. These ectopic testicles were almost invariably well developed anatomically. In striking contrast the true undescended testicles showed a high proportion of abnormalities, varying from failure of union of the body and the epididymis to actual absence of the body though the vas was present. He would suggest therefore that good results might be obtained, as regards fertility, by bringing the ectopic testicles down before puberty, whereas the true undescended testicle, because of some central failure, is often imperfect and its descended fellow might also be immature. Good results were therefore unlikely to be obtained by any form of treatment.

**Dr. V. C. Medvei** asked about the success rate of infertility clinics and how this was judged; secondly, how common was the deleterious effect from overheating of spermatozoa. A few years ago he had a patient who was a foreman in a factory testing the efficiency of refrigerators and spent eight or ten hours a day in an overheated atmosphere and a very low oligospermia developed. Three months after he had changed his work for a different environment his wife conceived.

**Dr. Swyer,** in reply to Dr. Medvei, said that the value of the fertility clinic was not wholly to be measured by its success in terms of pregnancy. The increasing number of these clinics reflected an increasing demand for the services they gave, one of which was simply to answer the question whether or no childbearing was likely.

The precise incidence of pregnancy amongst patients attending fertility clinics—as he preferred to call them, rather than infertility clinics—depended very much, of course, upon the extent to which the cases were followed up. It had been said that if all cases were followed up until the wife reached the menopause it was very likely that—in Liverpool, at all events, where these computations had been made by Dr. S. Bender—there would be 50% of pregnancies. He himself would not claim so high a figure, but he thought it was true that approximately one-third of the patients attending a fertility clinic had a fair chance of producing live children. It might be that some would say the figure should be nearer 40%. Of the remaining two-thirds it was very likely that half had no hope of childbearing at all. Thus it looked as if two-thirds of those attending the clinic were likely to be assisted either in furthering a pregnancy or in receiving a definite answer that pregnancy was highly improbable.

Although there was no doubt that the scrotum served as a thermostatic regulating device, it was well known that people who worked in hot atmospheres such as those of a bake-house, were liable to be infertile. Many practitioners would also have encountered men who wore suspensory belts for no very good reason and were sterile. It was a pernicious habit which should be discouraged.

**Dr. H. A. Davidson** said that it had been known for a long time that the scrotum was a thermoregulator, and in veterinary research in the 'twenties and 'thirties much work had been done along these lines. He quoted the classical work published by Phillips and Mackenzie who produced subfertility in rams by heat-insulating the scrotum.

In the human field insufficient attention had been paid to this matter although it had been shown that the human testis was normally maintained at about 2° C. below body temperature. When testicular temperature approached too close to body temperature the scrotal skin relaxed moving the testes away from the body and increasing the surface for heat loss by radiation and evaporation; conversely, if the testes cooled down too far the scrotum contracted, producing the reverse effect.

He had long been convinced that civilized clothing, and particularly suspensory bandages or a similar type of underwear interfered with the thermoregulatory function of the scrotum by keeping the testes close to the body and preventing heat loss.

He quoted the case which initiated his research along these lines. A man who had sperm counts of about 40 million per c.c. came back over a year later and produced repeated counts of between 2 and 5 million. There had been no intervening illness or treatment but he had started wearing a suspensory bandage soon after his first test. Six weeks after leaving this off the count had risen to 15 million, two months later to 45 million, and then his wife conceived. There had been several similar cases since, and he had not the slightest doubt that suspensory bandages could depress fertility, in some men at least.

He had then turned his attention to men suffering from varicoceles. For here the presence of a considerable volume of blood-filled veins in the scrotal compartment would tend to keep the testes near body temperature, and scrotal movements could not compensate for this. He had collected 6 successive cases of oligozoospermia whose varicoceles he had had operated upon. In 2 of these it was too early to tell the result. In all cases there had been several sperm counts before and several after operation in some cases. The first 4 cases showed the following results:

*Case I.* Number of spermatozoa per total ejaculate—before op. 47–52 mill.; after op. 250–360 mill.
*Case II.* Number of spermatozoa per total ejaculate—before op. 52–76 mill.; after op. 199–286 mill.
*Case III.* Number of spermatozoa per total ejaculate—before op. 90–96 mill.; after op. 172 mill.
*Case IV.* Number of spermatozoa per total ejaculate—before op. 20–36 mill.; after op. 256 mill.

The last 2 cases had not had time for further counts.

Usually it took three months from the operation before the improvement showed. This he attributed to the transitory depressing effect of the pyrexia following operation. Details of this short series would be ready for publication within the next two to three months.

**A Speaker** asked Dr. Swyer about the post-coital test. One heard different opinions as to this. On the one hand it was said to be valuable, and on the other to be quite useless.

**Dr. Swyer** thought the usefulness of the post-coital test depended on knowing how to interpret it. If it was done at the wrong time in the cycle, when the mucus could not be expected to be receptive, nothing was gained from it; but if done at the right time in the cycle and the findings were not consistent with the seminal analysis, it could reasonably be concluded that there was some coital inadequacy or else some inadequacy of sperm invasion or survival. If one interpreted the test along sensible lines one could get a good deal out of it. But if one were to prophesy on the basis of a negative post-coital test that pregnancy could not ensue, one was likely to be faced with many surprises.

**Mr. Howard G. Hanley** confined his remarks to 31 consecutive cases of azoospermia with clinically well-developed testicles, and with no evidence of any previous epididymo-orchitis. In 3 patients, tuberculous vesiculo-prostatitis was detected during routine rectal examination. In 3 more bilateral orchiopexy operations had been performed, and in the speaker's opinion, such operations had little more than cosmetic value (Table I).

TABLE I.—31 CASES OF AZOOSPERMIA WITH WELL-DEVELOPED TESTICLES AND NO EVIDENCE OF EPIDIDYMO-ORCHITIS

| | | | |
|---|---|---|---|
| Tuberculous prostate or vesicles .. | 3 | Absence of vasa .. .. .. | 4 |
| Bilateral orchiopexy operations .. | 3 | Blind ending vasa .. .. .. | 1 |
| Non-patent or atrophic vasa .. .. | 5 | Vaso-epididymostomy .. .. .. | 15 |

25 cases were surgically explored, and of these, 5 had non-patent or atrophic vasa. 4 had complete absence of any vasa, while one man showed a blind ending epididymis unjoined to an atrophic vas. There were thus 10 men with gross congenital lesions.

15 patients were subjected to vaso-epididymostomy, and of these, 4 had atrophic vasa on one side making bilateral anastomosis impossible.

At operation, if the epididymal tubules were seen to be distended under a glistening transparent capsule, they would generally be found to contain live sperms and the chances of success after anastomosis were very much increased. If these tubules were collapsed, or there were multiple cysts in the upper pole of the epididymis, the prognosis was poor, since the site of obstruction was probably too high for any anastomosis to be performed. (Slides were shown.) Such multiple cyst formation was found in 5 cases.

A summary showed that anastomosis was only possible in 15 of 25 cases operated upon, and in 5 of these the chances of success were small owing to cyst formation in the upper poles of the epididymides. Of the 10 cases where a distended epididymis was found containing live sperms, 4 had since shown a few sperms in the ejaculate following anastomosis. Therefore in spite of the fact that over 50% of these operations were doomed to failure from the start, exploration was considered worth while, since the patients were no worse off and some of them may have been greatly improved.

No success had resulted from the use of Hagner's original operation, but, during the past year, a modified technique had been used which had resulted in the 4 positive ejaculates already referred to.

**Mr. E. W. Riches** said that nearly ten years ago a Royal Commission on population was appointed and he had had the privilege of serving on the Biological and Medical Committee. One of the matters brought out was the small number of clinics in this country, particularly in London, devoted to the study of fertility. A vast change had since taken place; numerous fertility clinics had grown up, and they were being run by urologists in conjunction with gynæcologists as in his own clinic. There had been a great improvement in diagnosis and investigation and some improvement in treatment.

**Dr. W. M. Davidson** asked whether, as it had been suggested that there was a linkage between periods of infertility, increased tendency to abortion and the production of fœtal malformations, there was any danger that the artificial aiding of subfertile marriages might lead to the birth of deformed infants.

**Mr. David Band** considered it very important that a clinician should be in charge of clinics for infertility; these patients, after all, attended because they desired children and presumably they were the kind of people who would bring up their children properly and contribute usefully to the community. Therefore it was right that the problem of the infertile marriage should be considered with all the resources of the profession—the clinician, the endocrinologist, and the laboratory worker.

He had been impressed by Dr. Swyer's diagrams illustrating the inter-relationship of the various hormones which led to spermatogenesis. Supposing one testis were at fault and by its endocrine contribution led to an adverse reaction on the pituitary, might this lead to inhibition of spermatogenesis in the contralateral testicle? Possibly in such a case orchidectomy might be, in fact, the wisest treatment.

No mention had been made of the empirical treatment of infertility by hormones, and he hoped that Dr. Swyer in his reply would comment on the so-called androgen rebound, when improved spermatogenesis occurred after the cessation of testosterone therapy.

**Dr. Swyer,** in a general reply, said that he had, in fact, been engaged in analysing the outcome of pregnancy in women who had attended his fertility clinic and had completed their pregnancy either by aborting or going to term. Although these women seemed to show a statistically significant increase in the difficulties of labour of one kind or another—they had longer labours and more breech deliveries, for instance—he was glad to say that in a small series of cases (some 220 pregnancies) the stillbirth and congenital malformation rate of the babies born at term was as low as, or lower than, that of the 2,500-odd lying-in patients forming the control group at his hospital. It looked as though a woman going to the fertility clinic, once she became pregnant, might expect a slightly rougher time than her more fertile sister, but ought to produce as good a baby.

The incidence of abortions among the women attending fertility clinics was supposed to be high. In his series it was 19% whereas the incidence for all women at University College Hospital was only 3·5%. But these figures were not comparable, because in most cases abortions were treated out of hospital, and it was probable that there were a large number of abortions before the women got to the antenatal clinics. The figure for all spontaneous abortions might possibly be as much as 20%, so that the incidence among those attending the fertility clinic might not be so high after all.

In commenting further, **Dr. Swyer** thought the endocrinologist was not entirely to be blamed for the maltreatment of cryptorchidism. A boy of 9 who had had a course of hormone treatment without success should be handed over to a competent urologist straight away.

It was possible that one damaged testis might, by reason of its hormonal contribution, or lack of it, interfere with the other. That was a point which might be well worth studying, though the outcome was not too hopeful.

As for the use of hormones in defective spermatogenesis in eunuchoids with low F.S.H. output, chorionic gonadotrophin or testosterone appeared to be effective in some cases. They might, it would seem, even lead to cure, so that normal spermatogenesis continued on cessation of treatment. High doses of testosterone depress the testis and, as was well known, Heckel claims that on stopping treatment, a rebound phenomenon ensues, carrying the sperm density to levels far above those before treatment. This might be so but he had not yet observed it in his own patients subjected to this form of treatment.

**Mr. W. Selby Tulloch,** in reply, said that the President had told of having once made an exploration of the vas and finding it absent. This has been the experience of others including the speaker. He agreed with the view expressed by Mr. W. S. Mack that more active measures must be taken to avoid infertility associated with cryptorchidism. If the testes had not descended spontaneously by the age of 11 years, then operation should be done. He was very interested in Dr. H. A. Davidson's remarks regarding varicocele. Varicocele was a common cause of infertility. In the clinical examination of a person suffering from varicocele the testis—either one or both—was of normal size or slightly reduced in size and of soft consistence. This was probably due to a nutritional state. The speaker had drawn attention to this condition and had reported one case of azoospermia reversed by bilateral operation for varicocele—the case had a successful conclusion by the birth of a normal child to his wife (1952, *Trans. Edinb. Obstet. Soc.*, **104**, 17, 29). Many more operations had been performed, with considerable success, but it was not successful in all cases.

[*April* 23, 1953]

# Complete Inversion of the Bladder Through a Vesico-Vaginal Fistula of Twenty-Seven Years' Duration

By J. CHASSAR MOIR, F.R.C.S.Ed., F.R.C.O.G.
*Nuffield Professor of Obstetrics and Gynæcology, University of Oxford*

For many years my interest has been the treatment of vesico-vaginal fistulæ. I have now dealt with more than 100 such cases, the majority referred because of unusually difficult features, or because they had resisted previous attempts at closure. 64% of the cases were of gynæcological origin, and 36% of obstetrical origin. In this unselected series in which every case, save those with active carcinoma, has been dealt with,[1] I am happy to report that every fistula has been closed. Usually the functional result for the patient has been excellent; and this has been almost invariably so when the injury has been confined to the bladder itself. In those cases in which the urethra has had to be reconstructed I regret that the functional result has not always been so good, although usually there has been considerable improvement from the complete incontinence previously suffered. In this latter group there were 4 cases in which a transplantation of ureters was eventually advised or performed—4 cases out of a series of more than 100 cases of fistula. All the operations were performed by the vaginal approach, even in those cases in which a previous repair had failed. I may add that in many instances the previous attempts at repair had been made by the transvesical route.

One cannot see 100 referred cases of bladder injury without encountering some strange cases.

Remarkable amongst these was Mrs. C., a woman who lived up a Welsh valley, and who for twenty-seven years had had complete incontinence of urine. Her trouble dated from a difficult forceps delivery. She had had an operation for the treatment of the urinary leakage, but without benefit: regarding herself incurable she had resigned herself to a life of continual wetness. A simple calculation based on the data supplied showed that in this period of twenty-seven years she had washed and dried no less than 68,875 pieces of Turkish towelling.

It was remarkable that in spite of her disability this woman had two further pregnancies. During the second of these she became aware that there was "something falling down"—this "something" was diagnosed by the district nurse who confined her as a prolapse of the womb. In recent years the prolapse became more and more troublesome, and eventually drove her to seek further advice in a near-by medical centre. There it was found that the prolapse was no falling of the womb but a protrusion of the bladder itself—a turning inside-out of the bladder—through a large vesico-vaginal fistula. Through the kindness of Mr. Gareth Jones, the patient was sent to the Nuffield Department of Obstetrics and Gynæcology at Oxford.

Examination confirmed the reported findings. A large fleshy mass was seen at the vulva; it was as large as a fist, and at first sight had every appearance of a complete uterine procidentia. Closer examination showed that the mass was an inverted bladder (Fig. 1). The uterus and cervix were in the normal position. By suitable manipulations the mass could be replaced—although only temporarily—through the fistulous opening. The latter measured rather more than 1 in. in diameter, and was situated above the level of the urethra in the trigone of the bladder. Both ureteric orifices could be identified just within the margins of the fistula where they could be seen indulging, as is the wont of ureters, in a periodic urinary cascade.

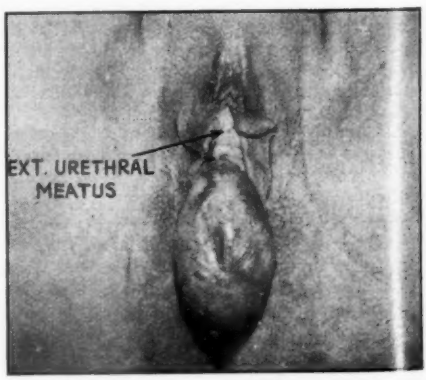


FIG. 1.—Inversion of bladder through vesico-vaginal fistula.

The whole of the prolapsed mass appeared to be covered with squamous epithelium. This fact was later confirmed by biopsy and histological examination.

Operative repair was surprisingly simple, and was accomplished by the vaginal route. The chief step in the repair was a series of nylon stitches inserted mattress fashion to approximate the vaginal edges. These edges had been prepared by a broad, slanting cut towards the bladder mucosa, together with a very slight undercut of the vaginal margins. The bladder was drained by continuous gentle suction through a urethral catheter for fourteen days. The sutures were removed on the twenty-first day.

[1]An exception is an Irish woman who returned to her own country without leaving any address.

The bladder function was quickly restored to normal, and the patient left hospital in excellent condition on the thirty-eighth day. A cystoscopic examination before discharge showed healthy-looking bladder wall, without any evidence of cystitis.

I have on 3 other occasions seen an inversion of the bladder through a vesico-vaginal fistula. In 2, the bladder was contained within the vagina and was seen, on speculum examination, as a deep red, velvety mass. In one other, the inversion appeared at the vulva, and simulated a cystocele. In the present case the mass protruded far beyond the vulva and was so large that it appeared, at first sight, to be a complete uterine procidentia.

## The Patient With an Advanced Carcinoma of the Bladder

By Noble Hudson, F.R.C.S.

*Late Senior Surgical Registrar All Saints' Urological Centre (Westminster Hospital Group)*

In the treatment of carcinoma of the bladder there are still considerable differences of opinion among surgeons and radiotherapists.

It has been stressed repeatedly (notably by Dr. Cuthbert Dukes and Mr. F. H. Masina) that in order to deal intelligently with the problem we must attempt to grade and classify bladder tumours and to seek relationships between the histological picture and extent of spread on the one hand, and the results of various forms of treatment on the other.

In general the results of treatment of bladder cancer are disappointing. Perhaps those who work with supervoltage irradiation are more hopeful but it does seem that at present many patients with advanced carcinoma of the bladder are refused this form of therapy either on the grounds that their cases are unsuitable or that the demands on the apparatus are too great. In any event, even if it should prove that supervoltage irradiation is the most effective form of treatment, there are not facilities for all bladder cancers to be so treated.

In 1950 Mr. D. S. Poole-Wilson said, "it seems that if a tumour has penetrated the bladder wall as far as the peritoneum, then the lymphatics are invaded beyond the bladder and all varieties of treatment are probably only palliative".

Dr. J. L. E. Millen of the Christie Hospital and Holt Radium Institute gave his results of treatment of bladder growths by irradiation. As I understand it, the more favourable growths were treated by radon seed implantation and the less favourable by deep X-ray therapy. In the group treated by deep X-ray therapy the five-year survival rate was as follows:

For non-infiltrating tumours 12% five-year survivals.
For infiltrating tumours 7% five-year survivals.

But Dr. Millen further stated that of 382 patients considered during the period under review, 96 (or 25% of the total) were beyond any attempt at cure. "60 were beyond any hope of treatment whatever." 36 were given a small dose of deep X-rays without any influence on the course of the disease. Death occurred in an average of four months.

Dr. J. M. W. Gibson also of the Christie Hospital and Holt Radium Institute said, "for the hopeless case no treatment at all is better than ill-judged radiotherapy". How true this is.

But what constitutes a hopeless case? What criteria should we use in deciding that a case is beyond any hope of treatment whatsoever?

While it is true that some patients with bladder carcinoma die a relatively comfortable death from uræmia or other cause, the majority pass their last few months in a miserable and degrading state with profuse hæmaturia, often with clot retention, strangury, pain, intensely increased frequency and sometimes continuous dribbling.

If a patient has left to him but a short span surely surgical intervention is worth while if it will render that span more tolerable.

In my view many patients are unnecessarily denied the benefit of a palliative cystectomy or even of a palliative ureteric transplant. Often the operability or otherwise of a bladder growth can only be determined by an exploratory operation. The presence of involved lymph nodes—be they even irremovable—is no contra-indication by itself to cystectomy.

It is unnecessary and dangerous to attempt to close the pelvic peritoneum after cystectomy because of the possibility of internal strangulation.

If we do not perform cystectomy in these cases what alternative measures are advocated?

Here I would like to express my thanks to Mr. S. I. Levy and Mr. Ralph Coyte for allowing me to operate on these their cases; however, they do not necessarily subscribe to the views just mentioned. I would like to thank also Professor James Pulvertaft for permission to borrow the specimens from the museum, Dr. J. H. O. Earle and his staff, then of the Gordon Hospital, for mounting the specimens and for the histological work, Dr. Cuthbert Dukes for much kindly and helpful advice and his technician at the Institute of Urology where the lantern slides were made for me.

The following cases I, II, III and IV were subjected to a two-stage cystectomy. Case V had a one-stage cystectomy. All the ureteric transplants were by the intraperitoneal Coffey method. In each case both ureters were dealt with at the same time.

In none of the cases was any attempt made to close the pelvic peritoneum.

*Case I.*—This is an infiltrating transitional-cell stage 2 carcinoma of an average grade of malignancy. The patient was a man aged 63. He had first noticed hæmaturia two weeks before attending hospital. On February 8, 1952, he had his transplant. Thirteen days later he was sent home. A month later he was readmitted. His cystectomy was performed on April 4, 1952. Twelve days later he was discharged. He was last seen on April 3, 1953, just a year after his cystectomy. He can hold his water for two hours by day and for six hours by night. A note was made that his liver was enlarged. He gets tired easily but otherwise he feels well.

*Case II.*—This is a stage 3 transitional-cell carcinoma of an average grade of malignancy. The patient was a man aged 68. He first attended on November 16, 1951, but declined operative treatment. Three months later he reported again with hypogastric pain and increased frequency. He said he was unable to get a proper night's sleep and he was now ready to have an operation. The growth had flourished exceedingly while he was making up his mind. He had his transplant on February 15, 1952, and his cystectomy on March 28, 1952. He was discharged on May 3, 1952. He later developed a pelvic mass and a suprapubic sinus leading deep into the pelvis and discharging foul pus. With drainage and antibiotics the sinus healed and oddly enough it remained healed until his death. The pelvic mass increased in size; it penetrated into his perineal pouch, it invaded his corpora cavernosa, it burst into his blood stream and disseminated widely. He died on December 13, 1952, eight and a half months after his cystectomy.

*Case III.*—This is a stage 4 carcinoma. It is an anaplastic transitional-cell carcinoma with a tendency to glandular metaplasia. It is of a high grade of malignancy and is spreading diffusely through the muscle. The patient was a morose man of 48. He first attended on October 9, 1951. After much delay and under pressure from his wife, he eventually submitted to operation in January 1952. By then he was having continuous hæmaturia with clots, continuous rectal and sacral pain with occasional sharp perineal pain. Urgency, dysuria, and increased frequency were present.

He had his ureteric transplant on January 18, 1952. He had his cystectomy on February 28, 1952. The glands on the left side were firmly adherent to the internal and external iliac arteries. No attempt was made to remove them. In May he reported that he was feeling pretty fit except for occasional backache. By July he was getting pains in the left thigh. In December he was examined by several surgeons. The mass of iliac glands had increased. There was no clinical evidence of local pelvic recurrence and no X-ray evidence of bony metastases. He was refused deep X-ray therapy (for all I know quite rightly). On Boxing Day he committed suicide, nine months after his cystectomy.

*Case IV.*—This is a stage 2 growth (Fig. 1). Histologically it is a transitional-cell carcinoma of an average grade of malignancy and with a tendency to squamous metaplasia (Fig. 2).

The patient was an old woman of 77. She was admitted on April 4, 1952. Her bladder was distended to her umbilicus. For three weeks she had noticed hæmaturia, increased frequency and pain.

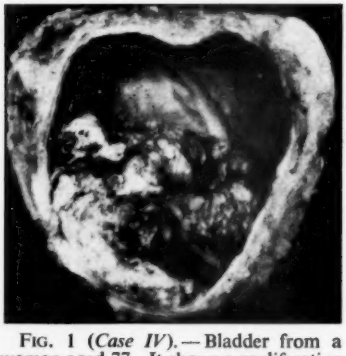

FIG. 1 (*Case IV*).—Bladder from a woman aged 77. It shows a proliferating stage 2 carcinoma.

FIG. 2 (*Case IV*).—Photomicrograph of section from growth shown in Fig. 1. This is a transitional-cell carcinoma with a tendency to squamous metaplasia. × 320.

On May 1, 1952, she had her ureteric transplant and three weeks later she underwent cystectomy. She stood both operations well. She had some difficulty with her anal sphincter but in October 1952 I timed her in the Out-patient Department and she was able to hold her water for two and a quarter hours. Every Saturday as was her wont she spent the evening in a "pub" from 7 to 10 p.m. and during that time she had to leave the saloon only once. On March 1 this year she died at the age of 78, ten months after her cystectomy.

*Case V.*—This is a stage 5 squamous-cell carcinoma of average grade of malignancy (Figs. 3 and 4), a man aged 66. As well as his carcinoma he had an enlarged prostate and two diverticula. He first

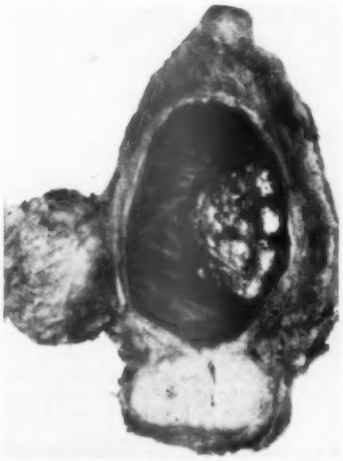

FIG. 3 (*Case V*).—Bladder from a man aged 66 years showing an ulcerative stage 4 carcinoma, benign hypertrophy of the prostate and two diverticula.

FIG. 4 (*Case V*).—Photomicrograph of section of lymph gland from the case illustrated in Fig. 3. This is a squamous-cell carcinoma of average grade of malignancy. × 280.

attended on April 4, 1952. He had first noticed hæmaturia two weeks previously. A one-stage cystectomy was performed May 1, 1952, and he was discharged fifteen days later.

Last seen in December 1952 when he reported that his control was good and he was still at work.

On January 9, 1953, nine months after his operation he died suddenly during the night.

It may be of interest to note that while this patient was in hospital his brother aged 64 attended the Out-patient Department with multiple papilliferous tumours of his bladder.

I think it was justifiable to submit these patients to cystectomy.

## Vaso-Epididymal Reflux Syndrome

By ALEC W. BADENOCH, M.A., M.D., Ch.M., F.R.C.S.

THE purpose of this short communication is to draw attention to a condition which is comparatively rare but which appears to be a definite clinical entity.

In May 1948, J. V. T., aged 60, consulted me complaining of pain in the left testicle. This pain had begun twenty-one days previously, was quite severe, gnawing in character and had lasted four hours. It recurred the following day and on most subsequent days, lasting usually for two to four hours. In between the attacks there was complete freedom from pain for anything up to twenty-four hours. A left inguinal hernia had been present for thirty years and for most of this time had been controlled by a truss—the latter had not recently been changed.

*On examination.*—There was nothing abnormal to feel in the abdomen. A left inguinal hernia which reached the neck of the scrotum was easily reducible. The left epididymis was rather tender and was enlarged to about twice the size of the right, both upper and lower poles being affected. On rectal examination, the prostate was moderately enlarged, bi-lobed, smooth and elastic. The urine was crystal clear and contained nothing abnormal. He had been seen by another surgeon, told that the hernia was the cause of his symptoms and was advised to have it repaired. Neither he nor his own doctor agreed with this course. I suggested that the pain

might be due to a reflux of urine along the vas deferens and advised further investigation, to which he agreed. During the waiting period he wrote me in the following vein "I am pretty sure now the pain starts invariably after I have passed water. I have got the habit of pressing two fingers down my groin, it may be pure imagination but I think this often prevents the pain from coming on. The pain is enough to make me lie in a hot bath for an hour or two and stops me doing anything. When the pain is over, my health is extraordinarily good."

*On investigation* the urine was sterile on culture. A cysto-urethroscopy showed some lateral and middle lobe enlargement of the prostate into the bladder. The verumontanum was small and nothing abnormal was noted in the appearance of the uterus masculinus or in the openings of the ejaculatory ducts. In view of the persistence and severity of the pain, I advised orchidectomy together with removal of the vas and repair of the hernia. From this he made an uneventful recovery. The pathological examination showed a great excess of fibrous tissue round the epididymis such as is found in a chronic inflammatory lesion. The vas was fibrotic and its lumen contained a coagulated colloid material. The testicle was normal. There was no sign of tuberculosis of neoplasm.

On January 16, 1953, I was asked to see S. S., aged 48, who had been admitted to hospital four days previously.

*History.*—He complained of recurring attacks of pain which he thought started in the lower part of the spine, passed round the waist and down into the scrotum. The pain first occurred some four years previously and at first came on infrequently. It began quite suddenly, was not accompanied by nausea or vomiting or with any disturbance of micturition. At times he felt the left testis might have swelled. Some two years ago the pain began to recur more frequently—every two to three weeks—and increased in severity. About eighteen months ago he was seen by a surgeon who found a left inguinal hernia, considered this to be the cause and did a repair. Six weeks after the operation the pain recurred exactly as before and since then there had been an attack every few weeks. He had been seen by at least five surgeons and had had the urine cultured on several occasions without anything abnormal having been discovered. The longest period of freedom from pain was six weeks and, during the last attack, the pain was so severe that he fainted and was admitted to hospital as an emergency. An intravenous pyelogram showed some dilatation of the left ureter down to about the middle of the sacro-iliac joint. It was in view of this that he was referred to me, with a view to having a catheter passed along the left ureter to exclude a ureteric calculus.

*On examination* I found the left epididymis was tender and was enlarged to three times normal size. The spermatic cord was a little tender and was thickened. On rectal examination the prostate was small, bi-lobed and smooth but on palpating in the region of the left vesicle the patient volunteered that the pain always started in this position and from there circled to the front. When asked, he said there was no relation between the onset of the pain and the act of micturition. I cystoscoped him and found nothing abnormal in the bladder or prostatic urethra and a ureteric catheter passed easily up the left ureter.

*Operation.*—I postulated that a vaso-epididymal reflux was the cause of the pain and advised epididymectomy. To this he agreed. The repair of the left inguinal hernia had been most efficient, however, and by the time I had exposed the pelvic part of the vas, the cord was somewhat attenuated. I performed an orchidectomy removing most of the vas deferens. He also made a good recovery. The section of the duct showed very little abnormal whilst the epididymis showed the appearances of inflammatory reaction without abscess formation.

*Discussion.*—The anatomy of the vas deferens is of course, familiar to us all. It is some 30 cm. long with a diameter of 2–3 mm. Towards its urethral end it dilates to form the ampulla and then narrowing joins with the duct of the ipsilateral seminal vesicle to form the ejaculatory duct. This very slender channel—2 to 3 cm. in length—passes through the prostate to open by a slit-like aperture on the lateral wall of the verumontanum. The wall of the duct is composed mainly of plain muscle with the outer layer longitudinal, the middle circular, and the inner layer again longitudinal. The mucous membrane is of columnar epithelium which in the human is not ciliated. I can find no reference to any sphincter mechanism at the orifice of the ejaculatory ducts in any of the commoner authoritative textbooks such as Gray, Cunningham, Buchanan, Scharper's Microscopic Anatomy, or Marshall (1922). Experimentally most observers have been unable to force fluid along the ejaculatory duct from the prostatic urethra. Bellfield and Rolnick found it impossible to produce a chemical epididymitis by injecting along the vas. Since Rolnick's work in 1925 and 1928, however, many urologists, if not all, have accepted that infection can pass along the lumen of the vas after prostatectomy and reflux of urine in this connexion is no new conception. Cases of fistula have been reported by Kreutzmann, 1938; Hanley, 1945; and Schmidt and Hinman, 1950. This occurrence may well be influenced by the point of division of the urethral end of the vas since if this occurs through the ampulla, and especially when there is also infection at the scrotal end, reflux may be more likely to occur. It occurs in association with genital tuberculosis and has been reported by Yates Bell (1937) and Perves and Duvergey (1939). It may then be due to the orifice being held open as the result of inflammatory rigidity.

It may follow obstruction in the urethra distal to the verumontanum and then should be bilateral.

J. W., aged 27, attended my out-patient's department in January 1947 with a suprapubic fistula.

*History.*—During the previous three years he had had fifteen operations on the bladder including excision of diverticula but had continued to leak suprapubically.

*On examination.*—There was 26 oz. of residual urine and a cystogram showed a grossly dilated prostatic urethra. I saw what I took to be a valve on each side of the prostatic urethra and removed part of them. After this the residual urine came down to 4 oz. the bladder closed and he was able to pass water fairly well but the urine remained infected with *B. coli*. In August 1949 he developed a moderately severe acute epididymitis. This partly cleared up but recurred in April 1950. He was again admitted to hospital and X-rays showed a reflux along both vasa. I tied the duct on each side but he developed a fistula on the left side, an abscess on the right and the suprapubic wound also broke down. I did a minimal resection in the region of the flaps and since then the fistulæ have remained dry. Such obstruction does not always produce vaso-epididymal reflux nor does it often occur in cauda-equinal lesions when the prostatic urethra may be widely dilated.

The 2 cases I described at the beginning of this communication do not fall into any of the above groups. There was a little prostatic obstruction in one case but this in itself, unless very asymmetrical, should not be the cause. Otherwise, in neither case was there any local ætiological factor and the urine was sterile in each case. On the other hand, Yates-Bell (1937) referred to a fistula having occurred in a patient who had had a cystostomy and vasectomy done for retention of urine due to prostatic obstruction. Vincent O'Connor in 1935 recovered from the vas, traces of a silver solution which had been instilled into the bladder the day before, in each of two cases of acute retention due to prostatic obstruction. Graves and Engel (1950) have produced epididymitis by injecting sterile urine along the vas in dogs. There seems little doubt, therefore, that urine can and does pass along the vas, in association with prostatic obstruction and may not always give rise to symptoms.

Many of us will also remember the numerous cases of epididymitis which occurred, sometimes in epidemic proportion, amongst Service personnel during the last war. I think it was Robinson in 1944 who first suggested that these might be due to reflux of urine from straining with a full bladder. At the time I felt that the more likely cause was a virus, but it was with this suggestion in mind that I made the tentative diagnosis in my first case. I have no suggestions as to why this reflux should occur, nor moreover as to why it should cause such severe pain; but I have no doubt it was the cause of the symptoms in each case. Both patients were extremely grateful. A year after I had operated on the first case, I received a telegram which read "Twelve months to-day you made a good job. Thank you." And in October of that year, and for several subsequent years, I received a brace of pheasants. It is only four months since the second case was treated, but up to now he is quite free from symptoms.

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## An Approach to the Problem of Simple Enuresis

By A. R. C. Higham, F.R.C.S.

The ætiology and the pathology of what I have called simple enuresis are both obscure if not unknown. Thus Ellison Nash in this country found that 86% of his cases had an unknown cause, and Campbell in America calls it a "purely functional disorder".

This is manifest, and I cannot frame a rigid definition that will include the older child who wets the bed and not the normal infant who would do exactly the same thing if not swaddled in absorbent nappies.

On the other hand, it is easy to exclude the pathological cases with continual dribbling or with obvious urinary obstruction preventing micturition from being instantly initiated, copiously continued, and completed with certainty, as it ought to be.

We are left with a larger group who are continent by day and who yet are emptying the bladder without waking, and it is these cases I wish to discuss.

If a child is capable of holding his water when awake he can be trained to hold it when asleep. This is fundamental. The mechanism, and the control of that mechanism, must both be intact if the child is dry by day. There can be no question of the nervous system being inadequate, under-developed, or deranged. A radiological diagnosis of spina bifida occulta is quite irrelevant in any clean dry child.

Children are not continent at birth. Education is called for, but domestic animals are house-trained without much difficulty. In the normal child nocturnal control develops two or three months after day control, but there is some factor, or group of factors, which prevents the enuretic from acquiring full control of the bladder sphincter.

The persistence of two bad habits lies at the root of the matter. The first is an infantile custom of frequent micturition, and the second is the power to pass water without waking. Frequent micturition encourages a small bladder capacity; this is unable to contain the produce of the night, and sleep is too deep to be interrupted by the minor sensation produced by passing water.

The truth of this is ascertained by measuring the volume of the bladder when micturition can no longer be delayed, and the figure arrived at is astonishing. There are many well-developed children who feel impelled to empty their bladders when they contain between 2 and 4 oz. These same children cannot be roused from sleep by ordinary stimuli, or do not awaken fully without unusual efforts.

Treatment should be directed towards increasing the bladder volume (Table I) and at the same time to waking the child when the bladder is becoming full and before the reflex of micturition is initiated.

The child must co-operate by holding the water until the stimulus to void is overpowering, so that the bladder is not emptied at the first desire to micturate but at the second or third. In this way, the capacity can be increased fourfold in a few weeks, and can be made greater than normal. As soon as the volume can contain the renal output for the night the artificial wakening is dispensed with, when the child at first wakes from habit and later sleeps dry all night.

A tablet or two of ephedrine, methyl ephedrine or amphetamine, will assist in completing the wakening of the child, but the parents must be warned that the drug will not, itself, cure enuresis.

I usually forbid fluids during the hour before bedtime, but rigorous deprivation of drink after tea-time just invites deception.

The parents take home the following summary:

(1) Measure how much the bladder will hold *now—ounces.*
(2) The child must hold his water *as long as he can by day.*
(3) Measure again after two weeks—*ounces.*
(4) He must *wake* up *before* the bed is wet—more than once if need be.
(5) Make him take the tablets every night to help him wake up.
(6) Measure again after another four weeks—*ounces.*

TABLE I

| Ages | Volume in oz. Before treatment | After treatment | Duration of treatment |
|---|---|---|---|
| 4 | 2½ | 10 | 3 months |
| 5 | 2 | 8 | 5 months |
| 6 | 4 | 11 | 5 months |
| 7 | 5 | 10 | 4 months |
| 8 | 3 | 17 | 3 months |
| 9 | 5 | 20 | 6 months |
| 10 | 6 | 14 | 3 months |
| 11 | 3½ | 12 | 6 weeks |
| 12 | 6 | 17 | 4 months |
| 13 | 3½ | 14 | 3 months |
| 14 | 6 | 17 | 4 months |
| 15 | 4 | 18 | 3½ months |
| 16 | 5 | 24 | 5 months |
| 17 | 7 | 12 | 2 weeks |
| 23 | 3¾ | 12 | 2 weeks—cured |
| 30 | 7 | 9½ | 2 weeks—cured |

# Section of Medicine

President—Sir ALUN ROWLANDS, K.B.E., M.D., F.R.C.P.

[*April* 28, 1953]

## DISCUSSION: UNUSUAL MANIFESTATIONS OF BRONCHIAL CARCINOMA

**Dr. Philip Ellman:** Few conditions in medicine have attracted greater attention or assumed more socio-economic significance than bronchial carcinoma. A generation ago it was considered a rare disease, although no doubt many cases then remained undiagnosed. To-day it is recognized as one of the most common forms of malignancy and in males is as frequent as carcinoma of the stomach or colon. World vital statistics show few more dramatic trends than the rise in the notified death-rate from this disease, while in England and Wales alone the number of deaths from carcinoma of the bronchus (13,233) in 1951 exceeded for the first time those from respiratory tuberculosis (12,036) (*see* Table I).

TABLE I.—LUNG CANCER AND RESPIRATORY TUBERCULOSIS
A COMPARISON OF DEATH-RATES FOR ENGLAND AND WALES, 1947–1951

| Year | Respiratory tuberculosis | Cancer of bronchus and lung |
|---|---|---|
| 1947 | 19,753 | 9,535 |
| 1948 | 18,798 | 10,463 |
| 1949 | 17,388 | 11,272 |
| 1950 | 14,084 | 12,232 |
| 1951 | 12,036 | 13,233 |

Further, by far the highest incidence was among males of the 40–60 age period. This constitutes an additional problem for the shift in age and sex distribution of pulmonary tuberculosis shows that the highest incidence and death-rate in males are likewise in the 50–60 age group. In females, on the other hand, the highest figures in pulmonary tuberculosis are for the 18–30 age groups. This is of significance as I hope to show later, when we come to consider the incidence of bronchial carcinoma in phthisical subjects.

The disease has, like pulmonary tuberculosis, an "asymptomatic" or "silent" as well as a symptomatic phase. In the asymptomatic group mass radiography, in spite of its limitations, is immensely valuable in detecting such clinically silent lung lesions, and should play a no less important preventive and diagnostic role than in the sphere of pulmonary tuberculosis. Ewarts Graham, in the U.S.A., showed in 1933 how early pneumonectomy could successfully treat the condition: (his patient, a doctor, is still alive and well twenty years later), and for prompt early diagnosis there must be increasing awareness of the condition, especially where males between 40 and 60 years of age are involved.

Cases of bronchial carcinoma exhibiting varied symptoms are referred to hospital; a large number will have symptoms referable to the chest. The condition may resemble any other acute or chronic infection of the lung and the onset is most often insidious, with perhaps a cough persisting without obvious cause; streaked sputum or hæmoptysis, unilateral localized wheezing, or dyspnœa may be significant features. The symptoms may be associated with obstructive changes, such as obstructive emphysema, atelectasis of a segment, lobe or even of the whole lung.

It should be emphasized, however, that physical signs may be completely absent, and at the same time a straight, technically satisfactory X-ray of the chest may be likewise negative, and yet a suspicious history demands further investigation. This may include X-rays taken on deep inspiration and expiration, and in various planes, tomography, bronchoscopy, investigations of sputum and bronchial secretions, and a barium swallow. Bronchography, kymography and angiocardiography may sometimes be of additional help.

The superadded secondary infection which often occurs may take the form of pneumonic and suppurative changes, presenting as pulmonary abscess, empyema, bronchiectasis, cavitating or miliary lung changes or it may assume the more insidious appearance of bronchitis, "influenza", pleurisy, and chronic pneumonia or the so-called "unresolved pneumonia". The dangers inherent in the complacent diagnosis of "unresolved pneumonia" cannot be too often reiterated.

There is one point I should like to make with regard to the supposedly rare involvement of the middle lobe. This is contrary to my experience, for in my series of cases I would have said that, for its size, the incidence of middle-lobe involvement is equal to that of other lobes of the lungs.

Cases which present with unusual manifestations and often without chest symptoms may be referred to various departments of a general hospital. Many of the protean manifestations arise because distant metastases may be present long before the pulmonary lesions cause symptoms, or physical, or even occasionally radiological, signs referable to the chest. The metastases do, in fact, first give rise to symptoms and the symptomatology may erroneously suggest: a neurological disorder, such as a brain tumour; a neuropathy or a pressure effect on either the brachial plexus or the cervical sympathetic, as in a Pancoast's tumour; a cardiac condition; Addison's disease with secondary involvement of the suprarenal; a locomotor condition, such as low back pain, shoulder pain, rheumatic arthralgias, joint swellings and even pulmonary osteoarthropathy and secondary deposits in bone. Throat conditions may also arise where hoarseness, loss of voice or dysphagia may be the presenting symptom; or even general medical disorders including pyrexias of unknown origin, "influenza", abdominal manifestations, &c., may be simulated.

In a series of 200 consecutive cases of bronchial carcinoma which I have observed in clinical practice, I shall make particular reference to (*a*) the asymptomatic group discovered by mass radiography (*b*) joint changes associated with carcinoma of the lung, e.g. pulmonary osteoarthropathy and polyarthralgias; (*c*) co-existent pulmonary tuberculosis and bronchial carcinoma; (*d*) carcinoma in relation to the pneumokonioses; and (*e*) a miscellaneous general medical group.

## Asymptomatic Bronchial Carcinoma

Numerous examples could be quoted to illustrate the need for grappling radically with opaque round shadows discovered by routine mass radiography, especially in males of the 40–60 age period. The "silent" phase of the disease may be prolonged for months or years without symptoms and many workers have found that early exploration of such cases by a thoracotomy—often the surest diagnostic measure—followed, where possible, by radical resection, frequently succeeds in avoiding spread of the carcinomatous process (Figs. 1 and 2). I agree strongly with Brock (1950) that just

Fig. 1.

Fig. 2.

Fig. 1.—X-ray chest (P.A.). C. P., male, aged 55, labourer. Symptom free. Small rounded homogeneous opacity (3 cm.) right lower lobe.

19.6.52: Thoracotomy followed by lobectomy; section showed anaplastic carcinoma arising in relation to an old tuberculous focus.

Following lobectomy: Uninterrupted progress. Excellent result. Maintained eighteen months later.

Fig. 2.—Same case as Fig. 1. X-ray chest (right lateral). Note opacity lying posteriorly.

as to-day we no longer expect to see a typical "consumptive" before diagnosing pulmonary tuberculosis so if a patient looks as though he may have malignant disease then his condition is almost certainly beyond repair. In short, *the better the general health and the shorter the duration of symptoms, the more hopeful the prognosis.*

### Joint Changes in Cancer of the Lung

*Hypertrophic pulmonary osteoarthropathy.*—6 cases in my series of carcinoma of the lung have presented with joint manifestations in the form of an acute or chronic polyarthritis as the initial complaint. 2 of these were referred as cases of rheumatoid arthritis and were associated with gross crippling. 4 complained of pain, swelling and stiffness in the joints, pain along the shafts of the long bones, swelling of subcutaneous tissues, including the nose and tongue in 1 case, and of the extremities in 3. Most of these cases had been treated for several months as rheumatoid disease and 3 had had low-grade fever but in none were there symptoms referable to the chest. These cases must, of course, be carefully differentiated from lung disease occurring in the course of an acute rheumatoid arthritis, i.e. "rheumatoid lung disease" (Ellman, 1947; Ellman and Ball, 1948).

The following is an outline of 2 of the 6 typical cases:

G. R., male, aged 53, was admitted to hospital in January 1947 as a case of rheumatoid polyarthritis. He gave a history of sudden onset of pain, swelling and stiffness of the ankles some twelve months previously, followed within a month by swelling of the fingers, ankles and toes. The hands were large and spade-like and the feet were massive. The swellings subsided after a month in bed and the patient resumed work in spite of disablement. Six months later recurring joint swellings aggravated his disablement and he had been obliged to give up his work three months before I saw him. He then presented the clinical picture of an acute rheumatoid arthritis. He was febrile (99°–101° F.); he had marked anæmia and lymphadenopathy but no splenic or hepatic enlargement. The joint changes included marked effusions into both knees and swelling of the wrists, fingers, elbows, left shoulder and ankles. There was marked limitation of movement of all involved joints and the condition was complicated by gross clubbing of the fingers and toes and thickening of the long bones. A clear amber-coloured lymphocytic fluid aspirated from the knees was sterile on culture and typical of a non-specific rheumatoid arthritis. There were no symptoms referable to the chest and clinical examination was completely negative. X-ray examination showed a well-defined rounded opacity 2½ in. in diameter, situated just above the

Fig. 3.—X-ray hands, wrists and right radius and ulna. N.B. (1) ossifying periostitis of radius and ulna. (2) osteoporosis and lack of definition of carpal bones together with tufting of terminal phalanges.

diaphragm in the posterior basal segment of the right lower lobe. X-rays of the bones showed, in general, considerable osteoporosis, together with pronounced ossifying periostitis of the long bones (Fig. 3).

Investigations confirmed the anæmia, the sedimentation rate was 42 mm. in the first hour (Westergren), the blood chemistry was normal. Bronchoscopy showed nothing noteworthy and the bronchial tree on both sides appeared normal.

A thoracotomy by Mr. R. C. Brock on 26.4.47 was followed by a right dissection pneumonectomy. The growth was palpated in the posterior basal segment of the right lower lobe, extending along the bronchi to the hilum. The day after operation most of the pain and swelling had left the joints and after forty-eight hours he had considerably more movement of all joints. He was, for example, able to close his fist completely, a thing he had been unable to do for six months. Within three weeks all joint swellings had disappeared although some pain and tenderness remained over the left knee. After six weeks he was up and about, self-supporting and completely mobile. Two months later, however, he succumbed. Post-mortem examination showed carcinomatous infiltration of the mediastinal glands and a carcinomatous nodule in the left fronto-

parietal region in the substance of the white matter. Section showed the growth to be an epidermoid bronchogenic carcinoma.

J. K., male, aged 55. Referred in 1944 on account of pain, swelling and stiffness of both hands, knees and ankles, with thickening of the long bones. The hands and feet were large, almost acromegalic, and the nose was likewise large. The condition was compatible with a rheumatoid arthritic lesion with marked effusion into both knee-joints. These were aspirated and examination of the joint fluid showed it to be characteristic of a non-specific rheumatoid arthritis. Within three weeks the fingers, toes and even the nose showed gross clubbing. The condition became complicated by gross pulmonary osteoarthropathy with, in addition to the joint and subcutaneous swelling, an ossifying periostitis of the radius, ulna, femora, tibiæ and fibulæ. There were no symptoms referable to the chest but radiological examination showed a fairly well-defined opacity in the

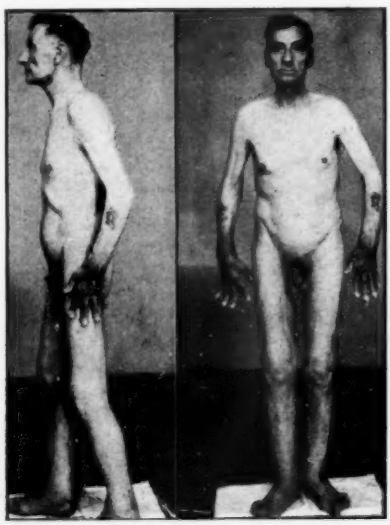

FIG. 4.—Showing joint, soft tissue and periosteal swelling.

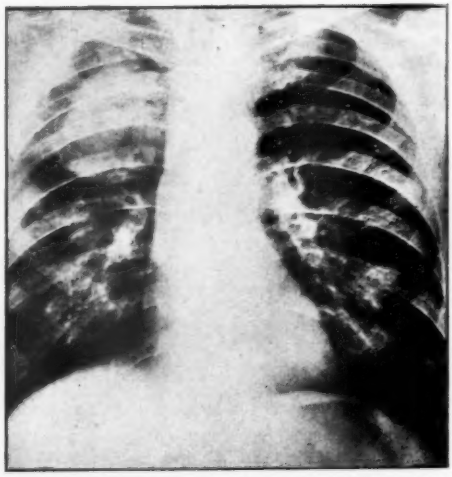

FIG. 5 (Same patient).—X-ray chest (P.A. view). N.B. Homogeneous opacity right upper lobe due to an anaplastic carcinoma.

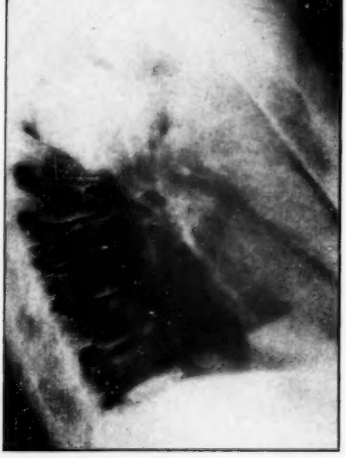

FIG. 6 (Same patient).—X-ray chest (right lateral). N.B. tumour lying in the posterior segment of the right upper lobe.

FIG. 7 (Same patient).—Photograph of the lung tumour, by courtesy of Mr. R. C. Brock. (Reproduced from the author's (1952) Essentials in Diseases of the Chest for Students and Practitioners, by permission of the Oxford University Press.)

posterior segment of the right upper lobe. The tumour was resected by Mr. R. C. Brock and proved to be an anaplastic carcinoma. The striking feature was that within forty-eight hours of its removal the joint swelling and the clubbing began to subside dramatically. The patient became progressively more mobile and two years later the joint and soft tissue swellings were practically negligible (Figs. 4, 5, 6, 7).

Consideration of these cases suggests strongly that arthralgias and arthritis of the rheumatoid type may be the earliest manifestations of hypertrophic pulmonary osteoarthropathy—the so-called Bamberger-Marie's disease which may itself be an initial symptom of an intrathoracic tumour. In none of my cases was there any real evidence of extensive tissue breakdown or appreciable infection, and the association of the joint and lung conditions on the basis of infection alone or of anoxia is difficult to explain. In this connexion it should perhaps be noted that the potential significance of the pituitary in relation to the ætiology of chronic rheumatoid disease has received some attention in recent years. In 2 of these cases there is a possible association between acromegaly and pulmonary osteoarthropathy, both, like rheumatoid disease, involving the mesodermal system. Large spade-like hands, swollen joints, increased size of bone due to increase in periosteal and subcutaneous tissues, are all features common to both conditions, a connexion noted by Fried (1948) in his work on lung cancer. He has suggested that the diffuse pulmonary osteoarthropathy of some cases is probably due to a dyspituitarism akin to acromegaly. The possible relation of endocrine imbalance with rheumatoid disease and pulmonary osteoarthropathy may have some significance although the pathogenesis of diffuse pulmonary osteoarthropathy is as obscure to-day as when it was first described by Bamberger and Pierre Marie in 1889 and 1890 respectively.

Crump (1929) postulates an abnormal substance circulating in the blood, affecting the periosteum, the bone, joints and soft tissues of the terminal phalanges as evidenced by clubbing of the fingers. Aschoff (1926) suggests that the lungs' "pulmonary glands" take on additional functions as secreting organs. The response to lung resection on diffuse pulmonary osteoarthropathy due to a bronchial carcinoma and the demonstration of the reversibility of pulmonary osteoarthropathy following pulmonary resection would appear to indicate that the causative factor arises from within the lung. In a recent study on 14 cases of hypertrophic pulmonary osteoarthropathy in pulmonary malignancy (Ray and Fisher, 1953), the tumour was located peripherally in 13 cases and the size of the tumour and the type of malignant cells played no apparent role in the pathogenesis of the osteoarthropathy.

### Co-existence of Bronchial Carcinoma and Pulmonary Tuberculosis

Perhaps the next unusual or atypical manifestation of lung cancer to discuss is the combination of bronchogenic cancer and pulmonary tuberculosis. I have personally observed some 8 cases in my series of 200, and have indicated that the highest incidence of both lung cancer and pulmonary tuberculosis in the male is in the 50–60 age period. An increasing number of such cases are being reported (Fried, 1935*a*; McCorkle *et al.*, 1942; Gerstl *et al.*, 1946; Farber *et al.*, 1949; Couts, 1951; Helm and Moon, 1952). Diagnosis of the co-existence of the two diseases is important because resection is the treatment of choice for both if one lung only is involved. It is, moreover, essential to keep bronchial carcinoma in mind, even though pulmonary tuberculosis manifestly exists, in males of the 50–60 age period. Symptoms and signs are often common to both conditions. A good response to bed-rest and chemotherapy favours tuberculosis. Radiologically, multiple shadows and calcification also favour tuberculosis whereas hilar opacities, paralysed diaphragm, erosion of ribs are more likely to occur in bronchial carcinoma. The differential diagnosis between tuberculomata and the rounded neoplasms is notoriously difficult and mistakes will inevitably be made. Exploratory thoracotomy should be encouraged in any doubtful case. Experience suggests that tuberculomata are more common in females of the 20–40 age group. In such dubious cases the sputum should be examined for malignant cells as well as for tubercle bacilli, and bronchoscopy is another diagnostic measure.

The once widely held belief that tuberculosis and bronchial carcinoma are antagonistic is no longer tenable. The increase of these cases in males between 50 and 60 is no doubt due to (*a*) the greater frequency of bronchogenic cancer and (*b*) the upward trend in the age distribution of pulmonary tuberculosis in the male.

Fried, (1935*b*) in a series of 319 cases of bronchial carcinoma, found some 11% associated with pulmonary tuberculosis. While the association of bronchial carcinoma with tuberculosis of the lung is of considerable clinical interest the possible ætiological relationship between the two is hypothetical and I would agree with Davidson (1951) in doubting any definite causal relationship, although Ewing (1935) holds the contrary view, and Raeburn and Spencer (1953) refer to the known tendency in many situations for chronic inflammation and fibrosis to precede malignant change in the lungs.

### The Pneumokonioses and Lung Cancer

Certain pneumokonioses have been incriminated as having a possible ætiological relationship with bronchial carcinoma. Pneumokonioses in Schneeberg miners and pulmonary asbestosis are well-known examples. Merewether (1949) has contrasted a figure of 13·2% of lung carcinomata in 235 cases of asbestosis with only 1·32% among 6,884 silicotic cases. In some 50 of my own cases of pulmonary asbestosis I am aware of 4 who have developed bronchial carcinoma; unfortunately

I have not been able to follow these up. Workers exposed to chromium compounds, nickel, arsenic and mica are said to exhibit increased incidence of lung cancer. In this connexion the following case is of unusual interest:

F. B., male, 54, was first referred to me on 5.7.48. For the previous forty years he had been a cobbler, a trade which exposed him to: (*a*) leather dust produced by grinding, and (*b*) road dust produced by forceful stripping of shoe soles.

He complained of moderate dyspnœa on exertion and a morning cough with scanty sputum. He felt well in himself and was not losing weight. Clinical examination showed his general condition to be good. He had gross clubbing of the fingers and toes but no evidence of pulmonary osteoarthropathy. There were no definite physical signs in his chest. There was no noteworthy lymphadenopathy and bacteriology of the sputum revealed no tubercle bacilli or other significant organisms and no neoplastic cells. X-ray examination of the chest showed a widespread diffuse reticulation of an almost miliary type throughout both lung fields, with some hilar adenopathy. I had regarded him as an undoubted case of dust reticulation but was unaware that leather dust was responsible for pneumokoniosis. His occupational conditions were kindly investigated for me by one of His Majesty's Inspectors of Factories and were reported as satisfactory. The dust to which he had been for so long exposed was confirmed as mainly leather dust. Many experts saw the films and agreed that whilst there was no evidence of silicosis the condition could be regarded as a dust reticulation, i.e. a pneumokoniosis probably due to his work. Careful assessment in hospital had excluded sarcoidosis.

For the next three years he remained fairly well except for increasing cough with dyspnœa in the winter. His weight was maintained, the physical signs were unchanged and the X-ray appearances showed no gross change. When he attended hospital in May 1951 his condition had deteriorated. He had lost 11 lb. in weight, was severely dyspnœic and cyanosed and complained, in addition, of dysphagia.

Clinical and radiological examination of the chest now showed evidence of massive collapse of the left lower lobe and within two weeks of the whole of the left lung (Fig. 8). I admitted him to my Chest Unit the same day.

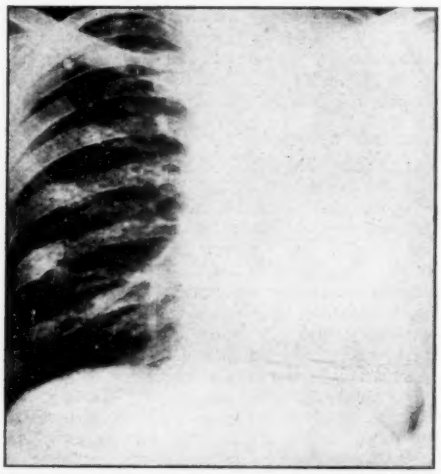

FIG. 8.—X-ray chest. Note (1) Miliary reticulation of the right lung; (2) Massive collapse of the left lung.

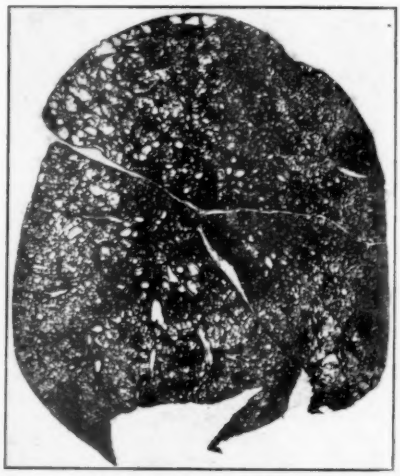

FIG. 9.—Specimen of the right lung showing honeycomb appearance with cystic spaces.

Bronchoscopy showed a typical neoplasm projecting into the lumen of the left main bronchus at the level of the carina. A specimen of sputum now revealed clumps of malignant cells and in March 1952 he died.

Dr. K. F. W. Hinson performed the post-mortem which revealed a bronchial carcinoma which had invaded and largely destroyed the left lung. The right lung, surprisingly, revealed a typical honeycomb appearance with cystic spaces, representing bronchiolectasis and emphysema, lying immediately beneath the pleura. Dr. Hinson has kindly provided me with a large section of the right lung (Fig. 9) and I am also deeply indebted to him for the photomicrographs (Figs. 10 and 11). His full pathological report is as follows:

*Histology.*—There is dilatation of the bronchi and particularly of the bronchioles with the formation of cystic spaces. These cysts are lined by a low columnar or cubical epithelium. Probably as a result of the acute terminal infection this epithelium has frequently desquamated. Chronic inflammatory exudation in the submucosa is absent. There is slight thickening of the alveolar walls, some of which have ruptured, forming emphysematous spaces. The amount of pigment in the perivascular and peribronchial lymphatics is small and is not associated with fibrosis. Pneumokoniosis bodies are not present (Figs. 10 and 11).

Leather dust is known to contain chrome, a substance which is regarded as carcinogenic. Health hazards in the leather industry seem worthy of future study and I know that Dr. A. I. G. McLaughlin, one of H.M. Inspectors of Factories, is engaged on special research in this sphere. There was no fibrosis

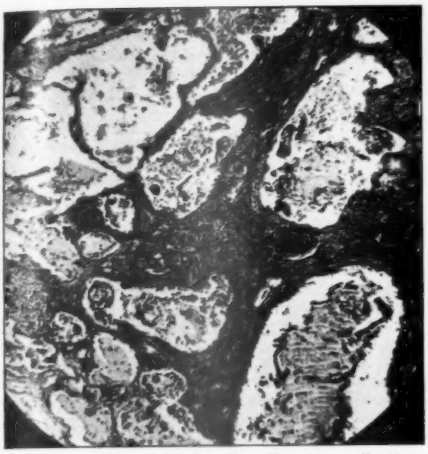

FIG. 10.—Histological section showing collections of cysts filled with desquamating epithelium and exudate in which there is some fibrous thickening of the walls. (Low power.)

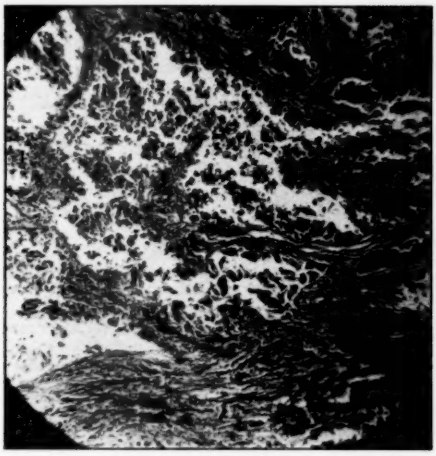

FIG. 11.—Histological section showing a carcinoma. (Low power.)

in this case but my own feeling is that the honeycomb lung may well have originated from the long-continued inhalation of dust.[1] Whatever one's view, this is certainly an unusual manifestation of bronchial carcinoma.

### CARCINOMA OF THE LUNG PRESENTING AS GENERAL MEDICAL DISORDERS

I have encountered a few unusual cases in association with general medical disorders: viz. 2 cases of lymphangitis carcinomatosa, with its characteristic radiological picture, presenting as "pyrexias of unknown origin" and "asthma", 2 cases presenting with "low back pain" with secondary deposits in the spine, several as "virus pneumonias" and a number with cardiac manifestations (auricular fibrillation, heart block, etc.).

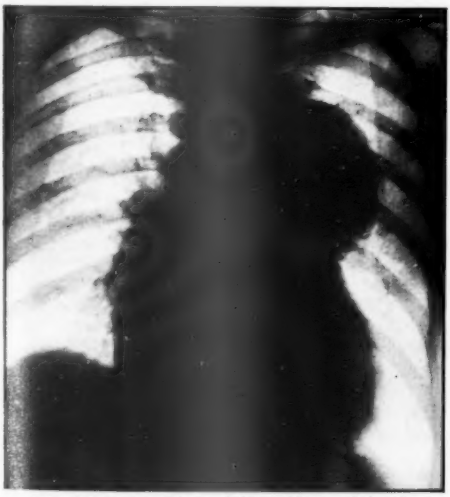

FIG.12 (Case W.W.,aged 46).—X-ray of the chest, showing gross cardiac enlargement due to pericardial involvement with a large dense opacity in the region of the left hilum.

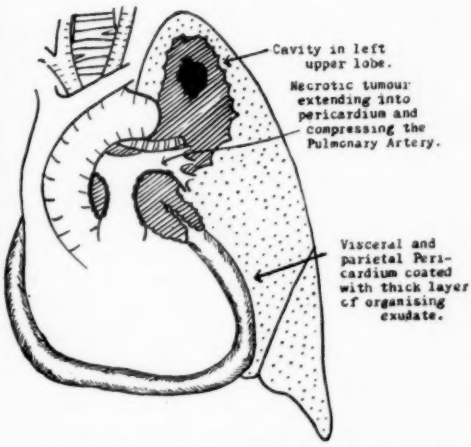
Cavity in left upper lobe.
Necrotic tumour extending into pericardium and compressing the Pulmonary Artery.
Visceral and parietal Pericardium coated with thick layer of organising exudate.

FIG. 13 (Case W. W., aged 46).—Line drawing illustrating the autopsy appearance of the heart and left lung.

[1] This viewpoint is confirmed by a communication I have had from Professor R. E. Lane of Manchester on the possible relationship of honeycomb lung to the inhalation of intense irritants over a long period.

The following case presented as an acute pericarditis:

W. W., aged 46, seen in 1936, gave a three weeks' history of sternal pain, breathlessness and high fever. Temperature range 99–103° F., pulse 120, respirations 28. His heart was markedly enlarged, his apex beat was just palpable in the 6th space 5 in. from the mid-line; heart sounds were muffled and he had obvious pericardial friction at the base of the heart. An X-ray examination of his heart confirmed the cardiac enlargement and showed an opacity at the left hilar region. He went steadily downhill and an autopsy by Dr. Norah Schuster showed a necrotic tumour arising from the left upper lobe bronchus with cavitation. The necrotic tumour extended into the pericardium along the visceral layer as far as the aortic and pulmonary valves. The rest of the heart was covered with a thick layer of organising inflammatory tissue. The pulmonary artery was compressed by tumour about ½ in. beyond its bifurcation. The tumour had invaded the wall of the artery but extended into the intima, except in the upper branch which was ulcerated. The rest of the artery was much narrowed (Figs. 12 and 13).

My last 2 cases are of interest from a therapeutic point of view:

W. B., male, aged 60, who was an old bronchitic and emphysematous subject, had a slight left hilar adenopathy when he was first seen in February 1949. His condition remained unaltered until January 1950 when he had some blood-streaked sputum. The physical signs and X-ray picture remained unaltered and his general condition was static. Nevertheless a bronchoscopy showed that while all the segments on the right side were normal, on the left blood was issuing from the upper lobe orifice. It had a granular appearance and biopsy revealed a well-keratinized squamous-celled carcinoma. It was considered inoperable and he was given radiotherapy from May 1950 until June of the following year. I saw him in February 1952 and two months later he chanced to hear he had lung cancer and committed suicide. At autopsy both lungs were found to be bronchitic and emphysematous. The hilar and tracheobronchial lymph nodes were not involved and the report was "no evidence of carcinoma now".

I have had a similar case of squamous carcinoma in a female, aged 53, involving the right upper lobe, which was considered inoperable but responded very well indeed to deep X-ray therapy.

The effect of deep X-ray therapy in these 2 cases of squamous-celled cardinoma is indeed striking. Dr. Joseph Smart tells me that he has had a series of similar cases of squamous carcinoma which have responded remarkably well to deep X-ray therapy.

## Conclusion

I have merely touched the fringe of this enormous problem. I have illustrated this subject of unusual or atypical manifestations by references to (*a*) the most important silent asymptomatic groups of cases which, from the prognostic point of view, I feel we must search out, especially in the 40–60 age period, with our mass radiography units, (*b*) the rheumatic arthralgias and pulmonary osteoarthropathies and their striking reversibility following pulmonary resection, (*c*) the group of cases of co-existing pulmonary tuberculosis and carcinoma of the lung, each commonly occurring in males at a similar age period, (*d*) lung cancer in relation to the pneumokonioses and (*e*) a miscellaneous group of cases of more general medical disorders, presenting as "pyrexias of unknown origin", possibly cardiac lesions, secondary deposits in bone, with, for example, low back pain, &c.

It will therefore seem that the whole of general medicine can be involved in the diagnosis of atypical manifestations of bronchial carcinoma.

[The author showed some 54 photographs illustrating atypical manifestations of carcinoma of the lung, 13 of which are shown here.]

I should like to add my acknowledgments and thanks for the surgical assistance I have received from Mr. R. C. Brock, Mr. T. Holmes Sellors, Sir Clement Price Thomas and Mr. Vernon Thompson, to Dr. K. F. W. Hinson for his help on the pathological side, and to Dr. J. H. P. Johnson for assisting me in collecting all my material for the preparation of this paper.

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**Dr. R. A. Henson:** It has long been recognized that carcinoma may be accompanied by neurological syndromes in the absence of relevant secondary deposits although it is only in recent years that the association has received much comment. These neuropathies are undoubtedly rare, but when they do arise the concomitant carcinoma is often situated in the lung; they are important because the neurological symptoms may antedate those directly due to the carcinoma by many months and even years.

We have seen 16 patients with carcinomatous neuropathy at the London Hospital, one in 1940 and the remainder since 1946; in 15 cases the underlying carcinoma has been found in the lung. This clinical material is highly selected and it is impossible to deduce from it the frequency with which neuropathies accompany carcinoma of the lung; there were, however, 4 cases of neuropathy (1·8%) amongst the 224 patients dying from carcinoma of the lung and examined post mortem during the fifteen years 1936–1950. Necropsies have been performed within the hospital on 6 of our patients, and it has been confirmed that the neurological manifestations under review were not due to secondary deposits; in the other cases it has been considered that secondary growths in the nervous system could be excluded on the clinical findings and course of the disease. 14 of our patients were male and 1 female.

The clinical manifestations of these neuropathies are varied; patients frequently show clinical and pathological evidence of multiple lesions in the nervous system, and there are symptoms which link the different clinical groups. We have therefore employed the general term carcinomatous neuropathy in diagnosis. Nevertheless it is possible to classify the various clinical pictures encountered on the basis of the sole or predominant disorder of function, and this approach is necessary to aid diagnosis. Our clinical material includes examples of subacute cerebellar degeneration, sensory neuropathy, polyneuritis and motor neuropathy or myopathy.

The following is a brief review of the clinical and pathological findings in our patients.

(1) *Subacute cerebellar degeneration.*—This form of neuropathy has been recorded as occurring in association with carcinoma of the breast, ovary, uterus and lung. The clinical and pathological aspects of the condition have been described by Greenfield (1934) and Russell Brain and others (1951). 2 of our patients fall into this group. The characteristic clinical picture is one of rapidly progressive ataxia and dysarthria. Diplopia may be an early symptom, and euphoria and dementia are often present. The neurological disorder may be polymorphic, pains in the limbs, sensory disturbances, deafness, atrophic paresis and pyramidal signs being encountered. The illness is usually of only a few months' duration but both our patients received early surgical treatment and survived for over two years. Our first patient was a typical example of the condition. This man, aged 56, presented with a two-months history of ataxia, dysarthria and diplopia. On examination he had gross cerebellar ataxia, bilateral extensor plantar responses and extreme euphoria. An X-ray of his chest showed a small opacity in the right lower lobe, visible only in the lateral view. A wedge resection of the lung was performed, and the lesion proved to be an oat-celled carcinoma of the lung. The neurological disorder progressed for six months by which time the patient was virtually decerebellate. There was no further significant change in his neurological state before he died from recurrence of his growth twenty-six months after the onset of symptoms.

The cerebrospinal fluid in this form of cerebellar degeneration frequently shows an increased content of cells and protein with a paretic Lange curve, but it was normal in both our cases. In neither patient was post-mortem examination made.

(2) *Sensory neuropathy.*—Denny-Brown (1948) has given an exhaustive account of the clinical and pathological aspects of this condition and has described the first 2 cases recognized. Dodgson and Hoffman (1953) have recently published a case occurring in association with carcinoma of the œsophagus. We have 3 examples. All our patients presented with paræsthesiæ and pains in the limbs and ataxia. Examination has revealed peripheral cutaneous sensory loss with impairment or loss of postural and vibration sense, sensory ataxia, loss of tendon reflexes and relatively little muscular wasting or weakness. The picture is predominantly one of sensory neuropathy, though one of our patients also had a moderate atrophic paresis and another had extensor plantar responses.

Neurological symptoms were initial in only one patient, but the neurological disorder had become established in each case before the diagnosis of carcinoma could be confirmed. The length of the illness varied from seven to eighteen months, death in each instance being due to the carcinoma or metastases. We were able to study the first patient for fourteen months. His neuropathy had progressed for four months when he was first seen, thereafter it remained stationary—being unaffected by pneumonectomy—until his death.

Two necropsies were made; in one patient there were intracranial metastases which were the cause of death, but both cases showed the degeneration of the posterior root ganglia described by Denny-Brown.

(3) *Polyneuritis.*—There are 2 patients under this heading. In each case motor and sensory disturbances in the limbs antedated pulmonary symptoms by a few weeks, the motor element predominating. The first patient had an almost complete and permanent remission of symptoms after

three months. The second patient had a mild dementia and extensor plantar responses in addition to his polyneuritis, necropsy showing no metastases in the nervous system.

(4) *Motor neuropathy and myopathy.*—The 8 patients in this group present a clinical picture which has not previously been recognized, though 2 of Lennox and Prichard's (1950) cases of polyneuritis are similar. The separation of these patients from those with polyneuritis is justifiable on clinical grounds. In 7 patients neurological symptoms preceded pulmonary complaints or the diagnosis of the carcinoma by periods varying from eight to twenty-eight months. In 2 of these patients the carcinomata were only discovered at necropsy, in spite of radiological examination of the chest shortly before death. The eighth patient developed his symptoms eleven months after lobectomy for carcinoma, and he is still alive.

The clinical picture has been remarkably constant. The patients suffered a progressive atrophic paresis which was often limited to or predominant in the limb girdles and proximal parts of the limbs, sometimes for considerable periods. The muscles of the neck and trunk were occasionally involved at an early stage. No fasciculation was seen. Bulbar palsy with dysphagia, nasal regurgitation of fluids and aphonia occurred in 3 patients, and these complaints were sometimes presenting. These symptoms were over and above any terminal dysphagia or aphonia due to the direct effects of the tumour. Ptosis and diplopia were also found. Tendon reflexes were diminished or lost in the area affected by paralysis and sometimes beyond it. There was sensory loss in only 1 patient though 6 complained of sensory symptoms; these symptoms were limited to muscular pains or cramps in 3 patients, but in the other 3 paræsthesiæ were also present. The pains were sometimes very severe. The predominant clinical picture was therefore one of a lower motor neurone lesion. Evidence of lesions elsewhere in the nervous system, apart from the sensory disturbances, was limited to extensor plantar responses in 4 instances and slight cerebellar ataxia in 1. The eighth patient differs from the others in that he has no clinical sign of any nervous lesion and the picture is that of a subacute myopathy or polymyositis. Muscle biopsy and electromyography have lent some support to the diagnosis of myopathy. It is possible that primary lesions of muscle have been present in other members of the group.

The course of the illness varied from eight to thirty-two months in the 7 patients who died. 5 patients had remissions of their symptoms. One patient had a dramatic though incomplete remission following pneumonectomy; relapse followed within four months and death from recurrences supervened. Another patient dated his remission from the institution of treatment with neostigmine at another hospital on a diagnosis of myasthenia gravis, one year after the onset of symptoms. His recovery was almost complete and lasted until his death from the pulmonary disease fifteen months later. The patient with a myopathic picture developed his neurological symptoms eleven months after lobectomy; he grew steadily worse for nine months when arrest and later considerable improvement took place. He is now working, thirty-eight months after operation, and has no signs of recurrence. Intensive vitamin therapy had been started two months before the remission began. Two other patients had spontaneous remissions which were briefer and less dramatic than the three quoted. Our present view is that the association of remissions with these various forms of treatment was coincidental.

Several patients gave a history of muscular fatigability suggestive of myasthenia gravis. The effect of injections of neostigmine was therefore investigated; the results were completely negative in 3 patients; 2 showed a temporary benefit which could not be reproduced when the injections were repeated or the drug was given by mouth.

Post-mortem examinations in 3 patients have confirmed that this disorder has not been due to secondary deposits. The differential diagnosis includes secondary carcinomatosis, motor neurone disease, myasthenia gravis, myopathy of late onset and dermatomyositis. Dermatomyositis is the condition which most closely resembles this syndrome.

*Pathology.*—The pathological changes in subacute cerebellar degeneration associated with carcinoma have been described by Greenfield (1934) and Russell Brain, Daniel and Greenfield (1951); they include loss of Purkinje cells from the cerebellum and degeneration in the spinocerebellar and pyramidal tracts and in the posterior columns. Greenfield (1934) also described the occurrence of "inflammatory nodules" in the spinal cord and elsewhere and perivascular and slight meningeal infiltration. We have seen this appearance accompanied by widespread loss of anterior horn cells in the cord of a woman with neuropathy associated with carcinoma of the breast, a picture of chronic anterior poliomyelitis. Milder changes of similar character were seen in one of the patients with motor neuropathy. 2 of the patients in this clinical group showed a loss of nerve cells from the motor nuclei of the cranial nerves and from the anterior horns with demyelination in the anterior nerve roots. Degeneration of the pyramidal and spinocerebellar tracts has also been demonstrated. Examination of wasted muscles has shown no constant picture, there has usually been a variable degree of fibre atrophy of uneven distribution. Our two patients with sensory neuropathy showed the loss of nerve cells in the posterior root ganglia with reflected degeneration in the peripheral nerves and posterior columns described by Denny-Brown.

The histology of the bronchial carcinoma is known in 12 instances; there are 9 cases of oat-celled carcinoma, and 1 each of anaplastic, anaplastic spheroidal-celled and tubular columnar-celled carcinoma.

*Discussion.*—Lennox and Prichard (1950) have shown that the association between carcinoma of the lung and polyneuritis is more than a chance one; there can be no doubt that this is even more true of the three other forms of neuropathy which have been discussed, although it is recognized that similar disorders either may or do arise in the absence of carcinoma. Whilst these syndromes are of great theoretical interest they also have a practical value. Their occurrence should lead to an intensive search for growth, especially in the lung. By the time our patients reached us the presence of bronchial carcinoma was known in 5; in 7 of the remaining 10 recognition of the neurological symptoms and signs led to early diagnosis of the underlying growth. The interval between the appearance of neurological symptoms and those due to the lung tumour may be upwards of two years, so that serial X-ray examinations are required to achieve diagnosis.

The time-relationships of the tumours and neuropathies in our patients make it exceedingly doubtful whether there is any direct causal relationship between the one and the other. Small or undetectable growths may be accompanied by profound neurological disorders which become arrested or regress as the growth enlarges. One patient developed his symptoms after the apparently successful removal of his carcinoma. These facts suggest that the ætiological relations of the neuropathy are with the carcinogen rather than with the carcinoma itself. The questions why neuropathy is so frequently found with bronchial carcinoma and why so few people with bronchial carcinoma develop neuropathy remain unanswered. Our investigations have so far yielded no clues. The resemblance of some of the neuropathological changes to those found in animals fed with deficient diets has led to the suggestion that the neurological lesions are due to a metabolic disorder. The inflammatory changes seen in some cases indicate that virus infection cannot yet be excluded as a cause.

Treatment is obviously directed to the underlying carcinoma. We have used full doses of vitamins, especially $B_1$, $B_6$, $B_{12}$ and E, in an attempt to relieve the neuropathies. We are not convinced that any patient has benefited from these ministrations.

I would thank my colleagues at the London Hospital for permission to include their patients in this report. Professor D. S. Russell has made the pathological examinations, and to her my thanks are also due.

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**Mr. T. Holmes Sellors:** A discussion on unusual manifestations of carcinoma of the lung gives a wide latitude to the speakers because it is impossible to say what are the usual or abnormal signs and symptoms. Admittedly cough, sputum, shortness of breath and so on are commonly recorded, but the earliest feature which gives any indication of the sinister process in the chest may not be among these features. From the point of view of the surgeon early diagnosis is essential if operative treatment is to hold out any hope of cure for these patients, and the fact that the progress of the disease is often slow should not be accepted as an excuse for tardy diagnosis. A period of anything up to two to three or even four years may elapse from the onset to final death in the absence of treatment, but the best chances for treatment lie in the early stages of the disease. Improved diagnosis has resulted from a greater awareness of the condition, particularly with the help given by radiology, but even so the figure of operable cases is probably in the region of 15 to 20%.

Everyone is aware of the unusual or freak manifestations when metastases are present and the exceptional case is sometimes over-emphasized to the exclusion of the more ordinary case. In order to try to give some sense of proportion I have analysed 200 consecutive patients admitted to Harefield Hospital with carcinoma of the lung and feel that these can be regarded as a sample of patients who are either sent for investigation or with a view to treatment. Advanced cases and patients not recognized as having the disease are naturally excluded, but the figure gives some idea of the proportion of symptoms which can be regarded as ordinary or exceptional.

Commenting on Tables I and II it will be seen that the disease can occur under the age of 40 and that the incidence of men to women is 10 to 1. The main features were respiratory and only a small proportion could be referred to other systems.

For the purpose of discussion a classification under the following headings can be considered:

(1) Constitutional effects.
(2) Signs and symptoms referable to the chest.
(3) Metastases.

(1) *Constitutional.*—Asthenia is common, particularly with large growths that usually break down, but it can also be due to toxæmia which results from pulmonary infection, which will be considered later. Persistent fever may occur with nothing to suggest involvement of the chest until a radiograph is taken. A high blood sedimentation rate is also common. Loss of weight may be extreme, but, *per contra*, the patients during investigation may actually put on an appreciable amount of weight.

TABLE I.—200 SUCCESSIVE CASES OF BRONCHIAL CARCINOMA

| *Age* | 21–30 | 31–40 | 41–50 | 51–60 | 61–70 | 71–80 | Total |
|---|---|---|---|---|---|---|---|
| Male .. | 1 | 3 | 36 | 78 | 59 | 5 | 182 |
| Female .. | 2 | — | 6 | 6 | 4 | — | 18 |

| | | | |
|---|---|---|---|
| *Site* | | | |
| Left main .. .. | 13 | Right main .. .. | 16 |
| Left upper .. .. | 50 | Right upper .. .. | 39 |
| Left lower .. .. | 43 | Right middle .. .. | 6 |
| | | Right lower .. .. | 33 |
| Total | 106 | | 94 |
| *Preponderating symptoms* | | | |
| Respiratory .. .. .. .. .. .. .. | | | 174 |
| General .. .. .. .. .. .. .. .. | | | 22 |
| Locomotor .. .. .. .. .. .. .. | | | 2 |
| C.N.S. .. .. .. .. .. .. .. .. | | | 1 |
| Gastro-intestinal .. .. .. .. .. .. | | | 1 |

TABLE II.—CARCINOMA OF LUNG

| | Presenting symptoms | | | Symptom frequencies | | |
|---|---|---|---|---|---|---|
| Cough .. .. | 55 | 27·5% | | 179 | 89·5% | |
| Pain | | | | | | |
| Pleuritic .. .. | 15 | | | 29 | | |
| Deep .. .. | 29 | 52 | 26·0% | 73 | 117 | 58·5% |
| Referred .. .. | 8 | | | 15 | | |
| Hæmoptysis .. .. | | | | | | |
| Staining .. .. | 30 | 37 | 18·5% | 85 | 95 | 47·5% |
| Gross .. .. | 7 | | | 10 | | |
| Dyspnœa .. .. | 19 | 9·5% | | 111 | 55·5% | |
| Radiological .. .. | 7 | 3·5% | | | | |
| Constitutional .. | 22 | 11·0% | | 83 | 41·5% | |
| Miscellaneous .. | 8 | 4·0% | | | | |
| Loss of weight .. | | | | 84 | 42·0% | |

Arthropathies in varying forms have been referred to in detail by Dr. Philip Ellman and in records of 20 to 30 cases we have found similar features to those he has described; and I can only add that this complication is most commonly associated with peripheral tumours which give few or no pulmonary signs.

(2) *Chest.*—The growth itself, if expanding steadily in the lung field, may produce no signs or symptoms for a long time, but it can and frequently does present as a pneumonia and, in this connexion, I would suggest that the term "unresolved pneumonia" should no longer be used since it has been often applied to growths beyond which there is infection and in which diagnosis has been unnecessarily delayed. Similarly, bronchial obstruction can lead to atelectasis, bronchiectasis and abscess formation, any of which may mask the cause. Sudden and severe dyspnœa if not due to atelectasis may be caused by a diffuse lymphatic spread of growth. In cases of doubt where an indefinite shadow in lung is observed a full course of antibiotic treatment should be given for two to three weeks and a further radiograph taken. During this time the sputum should be examined for malignant cells and also for tubercle bacilli. If at the end of this period there is little or no resolution serious consideration should be given to the possibility of a growth. If the shadow has regressed then a further period of delay is justified, but the patient cannot be discharged until the radiological shadow has completely disappeared. Obstruction of a bronchus can also give rise to a persistent wheeze which is sometimes only noted by the patient when he adopts a certain posture.

Hæmoptysis, though a frequent initial sign, is still too often ignored and many patients are told that they have strained themselves or have burst a blood vessel in the throat. No hæmoptysis, however slight, can be ignored; it is a red flag to be recognized by the whole medical profession. A massive hæmoptysis will almost certainly require full investigation, but small fresh streakings of blood on successive days is often neglected. Detailed investigation which includes radiology followed by bronchoscopy and possibly bronchography should be employed to try to discover the cause of the bleeding.

*Pleura.*—When a growth becomes adherent to the parietal pleura it usually spreads along the plane of the membrane for a considerable distance rather than breaking through the chest wall. A variable amount of pain is common and this is sometimes referred to the upper abdomen giving rise to a suggestion of a gall-bladder or ulcer dyspepsia. Pain referred down the left arm is sometimes confused with an anginal attack. A pleural effusion or empyema often gives rise to difficulty in diagnosis since the shadow of the fluid obscures the lesion in the lung. Routine investigation of the pus or fluid for malignant cells should be carried out, and in some cases of doubt a deliberate pleural biopsy is an important method of establishing diagnosis.

Brief reference can be made to the Pancoast type of tumour, usually regarded as a bronchial carcinoma in the limited area of the apex with special characteristics of painful invasion of the bone and of the brachial plexus and sympathetic chain.

*Mediastinum.*—Loss of voice by involvement of the left vagus or recurrent laryngeal nerve is a comparatively common early sign and is sometimes the presenting symptom without any suggestion of chest signs and symptoms. Paralysis of the phrenic nerve is only discovered on radiography and pressure of the growth on paratracheal glands or the superior vena cava is often overlooked in the early stages. Gross enlargement of glands may lead to displacement of the œsophagus with resultant dysphagia, and it is useful to bronchoscope patients with this complaint at the same time as passing an œsophagoscope. A fatal hæmatemesis has been seen as a result of a gland ulcerating into the œsophagus.

Pericardial infiltration may result in effusion, but the most important feature concerning the heart is sudden onset of auricular fibrillation in a patient whose heart rhythm has been previously normal. This occurs when the growth has spread along a pulmonary vein into the wall of the auricle, and it is significant that the diagnosis of the lung condition is often made in the first instance by the cardiologist. Confusion with aneurysm is sometimes encountered and even careful investigation may fail to differentiate this physical abnormality from a growth. A deep-seated substernal pain is a common symptom, and indeed twice as common as any other form attributed to carcinoma of the lung. It is possibly due to pressure and is usually present when there is an extensive involvement of the mediastinal structures by glands.

(3) *Metastases.*—Local or regional metastasis has already been dealt with, but the picture presented by distant secondaries is most varied. Secondaries in the brain are common and are often located in the frontal lobe where they give very few early signs or symptoms. A slight personality change requires careful neurological investigation, but in spite of this we have on two or three occasions proceeded to operation, the patient dying two or three months later of definite cerebral involvement which presumably was present before surgery was undertaken. Bone secondaries are often silent and spontaneous fracture is not common, though the pelvis and spine are sometimes involved and, in the absence of X-ray changes, in the early stages manipulation has been undertaken for supposed strain, but fortunately without harm to the patient. Enlarged glands are sometimes encountered in the neck and axilla and occasionally a skin nodule may be one of the earliest features. Metastasis in the liver is comparatively uncommon. One of the most interesting forms of secondary deposit is one which occurs in the suprarenal glands. Some patients have extreme weakness and pigmentation of skin, and we have encountered 2 cases in which a sudden and severe collapse occurred. This was thought to be due to pulmonary embolism but was found later to be caused by complete replacement of these glands by secondary growth.

Implantation in the small bowel has been observed on four occasions outside the series mentioned, in two instances it presented as an intussusception which was operated on.

*"Accidental" discoveries.*—Mass X-ray examination and routine fluoroscopy do lead to the discovery of a number of growths before there are any symptoms, but these cases are comparatively rare and it may well be found, if a careful history is taken, that the patient has been worried by some vague symptom which has not been reported to his doctor and that mass X-ray examination has been used in the hope of allaying his fears. Similarly some gastric and gall-bladder examinations are undertaken for pain which is really caused by the pulmonary growth; and again, backache and cardiac trouble may lead to the patient having the chest examined radiologically.

A great deal of responsibility for delayed diagnosis must remain with the medical profession; unusual or vague symptoms are not always studied sufficiently and the surgeon's experience is that the average time between these symptoms and the patient coming for actual treatment is anything between four and eight months; this is an improvement on the position ten years ago when the period was half as long again, but this is still far too long in the handling of such a disease.

[*May* 19, 1953]

## Neurological Sequelæ in Repatriated Prisoners of War from Hong Kong: a Follow-up. [*Abstract*]

By C. A. Clarke, M.D., F.R.C.P., and W. Sircus, M.D., M.R.C.P.

Dr. C. A. Clarke and Dr. W. Sircus showed two short films dealing with cases of nutritional neuropathy which had occurred in British prisoners-of-war captured at the fall of Hong Kong on Christmas Day 1941 and held there by the Japanese until 1945.

The first film had been made in Sydney in 1945 by the Medical Department of the Navy and the second taken at a follow-up in Liverpool in 1952.

The films showed the various aspects of the neuropathy and the follow-up demonstrated the following points:

(1) Scotomata, optic atrophy and macular degeneration all unchanged.

(2) Deafness—little change but more tendency to improve than the eyesight.

(3) Posterior column lesions—no change, except in a few mild cases.

(4) Peripheral nerve lesions—mild cases much improved and many recovered. Some severe cases also cleared up.

(5) Hyperæsthesia of soles—half recovered and half not (4 cases only).

(6) Lateral column lesions—1 case resembling motor neurone disease, unchanged.

It seems, therefore, that where the special senses and spinal cord have been damaged little recovery had taken place. Peripheral nerve lesions have, however, improved a good deal.

## Danish Novo Zinc Insulins

By J. M. Stowers, M.R.C.P., and J. D. N. Nabarro, M.R.C.P.

It has long been known that zinc is present in higher concentrations in the pancreas than in other organs, and in 1934 Scott stated that zinc or allied metals were necessary for the crystallization of insulin. The whole question of the inter-relation between insulin and zinc has been reinvestigated recently by Hallas-Møller and his colleagues at the Novo Terapeutisk Laboratories in Copenhagen. Their first important discovery was that phosphate, present as a buffer in some commercial insulins, had a greater affinity than insulin for zinc, and that if 0·01 M acetate buffer was used, very different results were obtained. If zinc insulin crystals are suspended in acetate buffer they are stable between pHs of 4·5 to 8, whereas if zinc insulin crystals are brought to body pH with phosphate buffer, the zinc leaves the insulin to precipitate as zinc phosphate while the crystals dissolve.

On injection of crystalline zinc insulin into man one might expect that the phosphate in the body fluids would have a similar effect, and that the preparation would have the transient action of a soluble insulin. However, the Danish workers found in dogs that this happened only slowly, and that the action of the insulin was markedly prolonged. The degree of prolongation depended on the size of the insulin particles. Thus zinc insulin crystals 100 microns long have a hypoglycæmic action lasting thirty or more hours in man, and the effect of smaller amorphous zinc insulin particles persists for twelve to fourteen hours. The size and form of the zinc insulin precipitate depends on the pH of the suspending medium, its zinc content, the temperature and the time. Between the pH range of roughly 5 to 6 the zinc insulin precipitate is wholly or largely crystalline. Outside this range the precipitate is amorphous. Furthermore the zinc insulin crystals once formed are stable in acetate buffers from a pH of 4·5 to 8. They therefore had two insulins, one consisting of crystalline zinc insulin and the other of amorphous zinc insulin in an acetate buffer, both of them stable at body pH. By mixing them it is possible to obtain varying durations of insulin action up to thirty hours or more. The crystalline long-acting variety is called "Ultralente", the amorphous variety with an action lasting twelve to fourteen hours is called "Semilente", and a preparation containing both crystalline and amorphous zinc insulin, which is claimed to have an action lasting about twenty-four hours, is called "Lente". Each variety contains nothing but three times crystallized insulin in combination with zinc and suspended in saline and acetate buffer, to bring the pH to 7·2. The amount of zinc present in each is 2 mg./1,000 units, the same concentration as in protamine zinc insulin. Each of the three varieties can be mixed with any of the others, but not with the current commercial insulins that contain phosphate.

We first heard about these insulins at the International Diabetic Congress in Leiden, July 1952. Dr. Hallas-Møller then kindly made arrangements with us for free trial supplies of

Novo zinc insulin to be granted to the diabetic clinic at University College Hospital, and the first consignment reached us in October 1952. The supplies have naturally been limited so we decided to restrict their use to diabetics needing more than one injection of the other insulins per day, and who had sufficient intelligence and training to be able to make a reliable comparison of the effects of a single daily dose of the new insulin with those of their former regime. Cases with a large insulin requirement have been particularly selected. We have also insisted that each case starting on the new insulin should do so in hospital, so that adequate laboratory and dietary controls could be made. Most of the cases started off in this way have continued to use the insulin under their usual living conditions at home so the final assessment has been realistic. 3 cases known to be allergic to commercial insulins have been particularly selected for trial with Novo zinc insulins, since these contain no added protein and are three times crystallized in the course of their preparation. Investigation in hospital has been undertaken as follows: the patient is given a diet which is characterized by a relatively small breakfast, a small mid-morning snack, a relatively large midday dinner and tea meal, and an average-size supper and small bed-time night-cap. The total calorie value has usually been slightly less than that of their normal workaday diet, since in hospital their exertion is limited. In Figs. 1–3 the meals are shown as blocks based on their glucose equivalent. This is calculated by

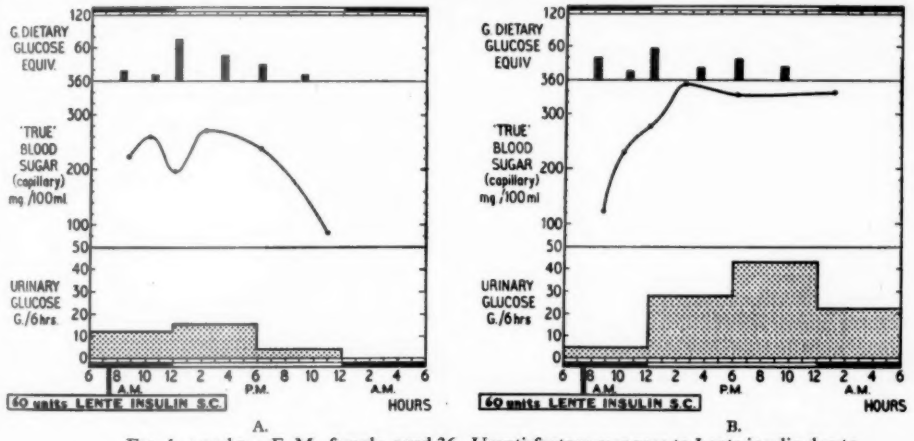


FIG. 1, A and B.—E. M., female, aged 36. Unsatisfactory response to Lente insulin due to spontaneous variation by patient.

adding the grammes of carbohydrate in each meal to 58% of the grammes of protein and 10% of the grammes of fat, since these proportions on the average are converted by the body to glucose. The remainder of the diet is ignored in the diagrams since it is not so directly concerned with the insulin requirement. The blood sugar has been estimated by the Somogyi-Nelson true blood sugar method on capillary blood and has been carried out in duplicate at six different times in the day as shown in Figs. 1–3. The urine has been collected in four six-hourly specimens and if the qualitative Benedict's test for sugar has been positive a quantitative Benedict's estimation has been performed, the results being shown as a block histogram on the baseline of the charts. Whenever a change of diet or insulin has been made a full day has been allowed to pass before these estimations of blood and urine sugar have been started. The number of such investigative days allotted to each patient has varied from one to five. In every case the insulin has been given forty-five to sixty minutes before breakfast. One striking result of these detailed tests of diabetic control is the great individual variation of response by patients to the same regime of insulin and diet. When given the Lente insulin which is claimed to act for twenty-four hours, some cases have shown a quick but transient fall of blood sugar while others have experienced a delayed one. There are occasional unfortunate cases who show both of these responses on different days, and indeed the only 1 of the 14 cases in the trial in whom control by Novo zinc insulins proved unsatisfactory was such a case (Fig. 1). It is clear that no one-shot insulin will ever satisfactorily control cases with such wide variations in response. Fortunately they form a small minority. Another consequence of this unpredictable factor of individual response is that a suitable mixture of delayed action insulins has often to be prescribed to suit an individual's needs. Thus of the 14 cases, so far studied only 3 have been well controlled by injections of Lente insulin alone, and, in general, these 3 have needed a relatively small dose, the largest being 48 units. All the remaining cases, apart from the one who was considered unsuitable for any one-injection regime, have needed Lente plus an admixture of a variable proportion of Ultralente insulin. These proportions have varied from 5 : 1 Lente : Ultralente, to 2 : 1. The mixture of

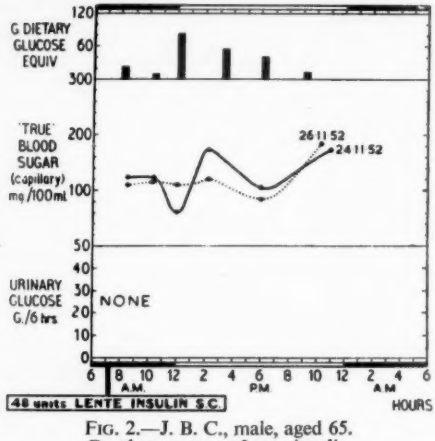


FIG. 2.—J. B. C., male, aged 65.
Good response to Lente insulin.

insulins in a syringe is a technically difficult procedure to perform satisfactorily especially if there is any impairment of vision, and we have therefore supplied these patients with insulin pre-mixed in suitable proportions in sterile vials. Patients who previously had as many as three injections a day, often of two different insulins, greatly appreciate this simplication in their routine. There seems to be less danger of nocturnal hypoglycæmia than on treatment mainly with protamine zinc insulin, and the hypoglycæmic reactions seen during the day have not been severe and have simulated those caused by Globin insulin. One case has taken 200 units/day and two have taken 120 units. As we mentioned earlier 3 of the 14 cases showed local skin sensitization to Globin or protamine zinc or soluble insulin, necessitating in one case the daily administration of Phenergan, but none has shown any evidence of sensitivity to the Novo zinc insulins.

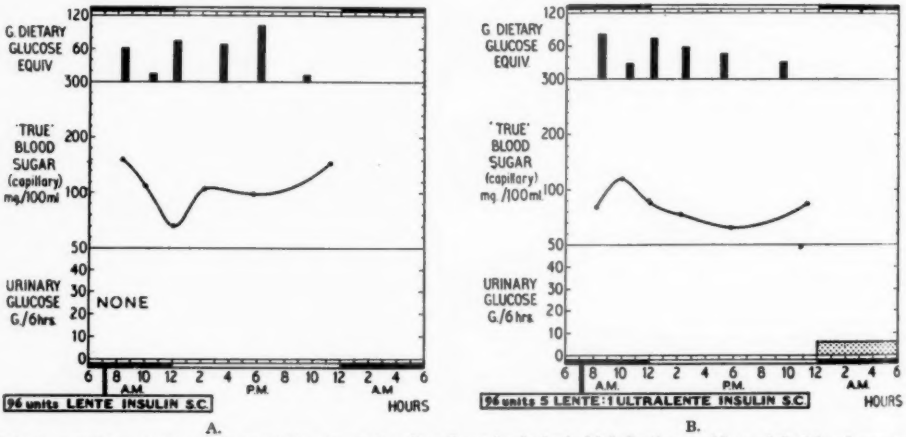


FIG. 3, A and B.—S. R., male, aged 36. Lente insulin allowed relatively high fasting and late night blood sugars, corrected by mixing 1 part Ultralente to 5 parts Lente.

Since the first introduction of soluble insulin many modifications of insulin have been tried and most have been discarded, so it is wise to be cautious in assessing the newest arrival. With the three types of commercial insulin already available in this country it would certainly complicate matters to introduce an additional three varieties of zinc insulin. The questions to be answered are first, whether the Novo zinc insulins have material advantages over the currently used insulins, and second, if this is conceded, whether the Novo zinc insulins can entirely replace any of those now supplied. We believe the new insulins are better than the varieties in current use, although our personal experience is not yet adequate to justify such a conclusion. We say this because the Novo zinc insulins have been found in large scale trials in Denmark to be suitable for the treatment of 90% of all diabetics by one injection daily, and allergy to these insulins has not so far been reported. The nearest approach to this achievement is that of NPH insulin which has a duration of action which suits a high proportion of diabetics when given once daily. If its action proves too prolonged it can easily be shortened by mixing it with soluble insulin, but if its action proves too short there is no way of lengthening it. Here lies one of the main advantages of the series of Novo zinc insulins, which can be graded over a wide range of action. If the Novo zinc insulins are superior even to NPH insulin, they could presumably replace both Globin and protamine zinc insulins. If this were done, there would be a strong argument for using soluble insulin which contained no phosphate so that it could be mixed with the Lente or Ultralente varieties. British soluble insulin already has no added phosphate as finally dispensed. These three insulins would seem to cover all needs.

# A Syndrome of Erythema Nodosum, Arthritis and Bilateral Hilar Gland Enlargement

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ERYTHEMA NODOSUM is believed to appear as an allergic reaction to a variety of known toxic and infective agents. 5 cases of unknown ætiology, but with a somewhat characteristic clinical picture have been seen during recent years and have been followed for periods ranging from two to five years.

Onset has been sudden and clinical recovery complete in a matter of weeks. The patients have suffered from fever, erythema nodosum and arthritis. X-rays have shown a smooth, largely symmetrical, bilateral hilar gland enlargement, often of considerable size; the broncho-pulmonary group of glands is often involved, standing out rather characteristically from the mediastinum (*see* Fig. 1). Resolution is complete within a few months. Recovery has been maintained.

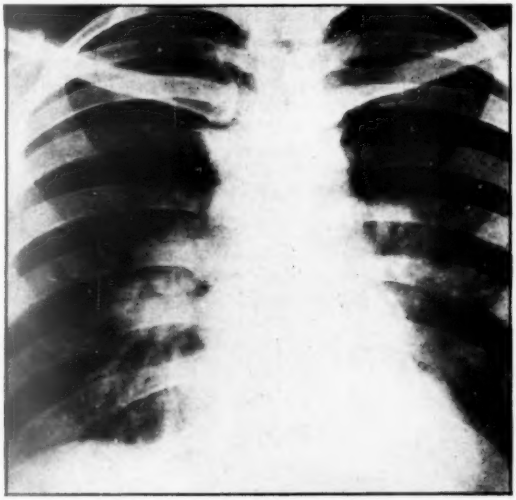

FIG. 1.—X-ray of Case 1 showing bilateral hilar gland enlargement.

Respiratory or other symptoms (except in Case 5), splenomegaly, lymphadenopathy and iritis have not been recorded. Parenchymatous lung changes have not occurred. Tubercle bacilli have not been found. White blood counts were made in the first 4 cases and found normal. X-rays of the hands in the last 3 cases have shown no abnormality.

## CASE REPORTS

*Case* 1.—W. B., female, aged 29. Onset March 1946. Erythema nodosum of shins and forearms. Arthritis of right knee, ankles and shoulders. Fever for eight weeks. Mantoux reaction 1 : 100,000 weakly positive. X-ray two months from onset showed bilateral hilar gland enlargement. The next X-ray seven months later was virtually normal. Patient well and X-rays remained normal for five years.

*Case* 2.—M. W., female, aged 31. Onset March 1948. Erythema nodosum of shins. Arthritis of elbows and carpometacarpal joints of both thumbs. Fever for two and a half weeks. Mantoux reaction 1 : 10,000 strongly positive. X-ray shortly after onset showed bilateral hilar gland enlargement. X-ray four months from onset was virtually normal. Patient well and X-rays remained normal for four and a half years.

*Case* 3.—P. C., female, aged 32. Onset August 1950. Erythema nodosum of shins. Arthritis of knees and right ankle. Fever for eight weeks. Mantoux reaction 1 : 10,000 only weakly positive. X-ray one month from onset showed bilateral hilar gland enlargement and calcified areas in both hilar regions. An X-ray five months from onset was essentially normal. Patient well and X-ray remained normal for two and a half years.

*Case* 4.—D. F., male, aged 24. Onset June 1951. Erythema nodosum of shins. Arthritis of ankles. Fever for seven weeks. Mantoux reaction 1 : 100 positive, higher dilutions negative. X-ray one month from onset showed bilateral hilar gland enlargement. Considerable resolution seen at four months, complete at seven months. Patient well and X-rays remained normal for two years.

*Case* 5.—E. S., female aged 55. Admitted to hospital under the care of Dr. R. Kempthorne. Onset April 1951. Patient complained of frequency and dysuria. Erythema nodosum of shins. Arthritis of wrists. Urine contained pus cells and *B. coli*. Fever for five weeks. An X-ray two weeks from onset showed bilateral hilar gland enlargement and a calcified primary focus in the left lower zone. An X-ray three months from onset was still definitely abnormal, but one three months later was normal. Patient well and X-rays remained normal for two years.

## Cases from the Literature

Cases with this syndrome have been reported by Kerley, 1942; Forssman, 1946; Bonnet, 1946; Lofgren, 1946; Vogt, 1946; Middlemiss, 1949; Sterling, 1950; Johnson, Hanson and Good, 1951; Dunner and Hermon, 1952.

Females have been affected more often than males, and the age incidence has ranged from 19–61. Mantoux reactions have been negative in the majority. The follow-up period in many of these cases was comparatively short, and this makes an opinion on their ætiology more difficult.

Incomplete forms of the syndrome probably exist, as exactly similar cases, except for the absence of arthritis, have been reported by several of the above authors.

## Ætiology

The age range, the comparatively rapid resolution of florid hilar lesions, negative or only weakly positive Mantoux reactions, and calcified pulmonary lesions (in 2 of our cases) are points against the diagnosis of primary tuberculosis.

The absence of recorded upper respiratory or other infections in most of these cases is against the diagnosis of streptococcal erythema nodosum, or undulation in tuberculin sensitivity due to intercurrent infections. Gross hilar gland changes without parenchymatous lesions are difficult to reconcile with the former explanation, and negative or only weakly positive Mantoux reactions with the latter.

Sarcoidosis must receive more serious consideration. Little is known about the pathology of these cases and such an explanation cannot be excluded; this applies particularly to those cases in which observation periods have been short. Boeck's sarcoidosis is usually thought of as a chronic illness with manifestations appearing at intervals for years. Cases with the present syndrome in which recovery has been long maintained, therefore, present a special problem. If sarcoid changes were to be demonstrated in such cases it would be necessary to postulate either an acute completely recoverable form of Boeck's sarcoidosis, or another agent capable of causing such changes. That sarcoid change may be a pattern of reaction to a variety of agents seems to be favoured by modern opinion (Scadding, 1950).

It is possible that the condition is a disease *sui generis*. In favour of such an explanation is the rather characteristic clinical picture presented by these cases.

We are indebted to Dr. R. Kempthorne for permission to report on Case 5, and to Mr. C. W. Hall for the reproduction of the X-ray in Fig. 1.

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**Dr. Bernard Freedman:** [*Abstract*].

My patient was a housewife, aged 29. Her illness started in May 1952 with much pain in the knees and ankles, spreading a month later to the wrists and shoulders. Seven weeks after the onset she developed erythema nodosum. The Mantoux 1/1,000 was strongly positive. Radiograph of the chest showed considerable bilateral enlargement of hilar glands with no changes in the lung fields. The arthritis cleared up completely as the erythema nodosum faded. The hilar gland enlargement remained unchanged until the middle of the eighth month of her illness, that is five months after the enlargement was first discovered. Two months later the appearances had returned to normal. Total duration of hilar gland enlargement lay between five and seven months. Throughout the disorder there was malaise, lassitude and elevation of E.S.R., but no pyrexia, tachycardia or respiratory symptoms. [Radiograph was shown.]

# Section of Odontology

President—E. WILFRED FISH, C.B.E., M.D., F.D.S. R.C.S.

[*March* 23, 1953]

**Fibroma of the Maxilla.**—A. E. W. MILES, F.D.S., L.R.C.P., M.R.C.S.

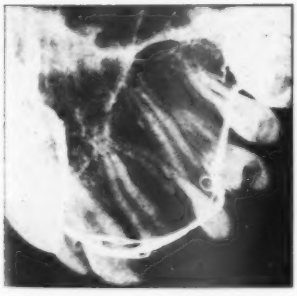
P. S., male, aged 11 years.

18.7.50: Presented with an elastic painless rounded swelling about 2 cm. diameter in the labial sulcus in $\underline{|2}$ region. It was first noticed two years previously and had gradually increased since. Radiographs showed a rounded area of translucency with a moderately well-defined margin centred between the roots of $\underline{|1}$ and unerupted $\underline{|2}$ which appeared to be displaced by the lesion (Fig. 1).

The diagnosis of globulo-maxillary cyst was made in spite of the fact that typically such cysts occur between the maxillary lateral incisor and canine. Globulo-maxillary cysts are presumed to be of similar origin to the alveolar clefts associated with cleft lip which it is well known may pass between the central and lateral incisors. At least one globulo-maxillary cyst in this situation has been described (Roper-Hall, H. T., 1938, *Brit. dent. J.*, **65**, 405).

At operation a smooth-walled cavity was found with a thick loosely attached lining of firm tissue with only a small central cavity. This tissue was enucleated and the bone cavity allowed to heal by granulation. One year later the cavity was almost obliterated and $\underline{|2}$ was erupting. Regeneration of bone is now complete and there is no evidence of recurrence (Fig. 2). Under the care of Mr. H. E. Wilson an appliance is being used to bring $\underline{|2}$ into position in the area.

FIG. 1.—Pre-operative radiograph.



← FIG. 2.—Radiograph two years and four months after operation.

FIG. 3.—Section stained hæmatoxylin and eosin. × 82. A, blood vessels surrounded by whorls of collagen fibres. B, fibres staining deeply with hæmatoxylin.

On section the tissue proved to be composed of a disorderly arrangement of bundles of connective tissue fibres among which is a good deal of mucoid material. Some of the fibres stain deeply with hæmatoxylin and with mucin stains. This unusual staining reaction is probably due to a concentration of cement substance or mucoid material on the surface of the fibres rather than a degeneration of the fibres themselves. The central cavity has no epithelial lining and was probably produced by complete degeneration of the centre of the mass. The larger collagen bundles appear to be centred about vessels and the mucoid material and hæmatoxylin-staining fibres are mostly between these compact collagen bundles (Fig. 3). No nerve fibres could be demonstrated in the tissue in silver preparations.

**Peripheral Fibro-osteoma of Mandible.**—B. W. FICKLING, F.R.C.S., F.D.S., and R. B. LUCAS, M.D., M.R.C.P.

G. A., boy, aged 12 years. Bony swelling of left mandibular ramus. Radiographs showed circumscribed mass with appearances suggesting chondroma. Removal by intra-oral approach and suture. Healed in ten days.

*Pathology.*—Bony mass 1½ in. in diameter and pedicle ¼ in. long. Microscopically, collagen bundles, cellular connective tissue, osteogenesis and bony trabeculæ all intermingled.

**Complex Composite Odontome of Mandible.**—B. W. FICKLING, F.R.C.S., F.D.S., and R. B. LUCAS, M.D., M.R.C.P.

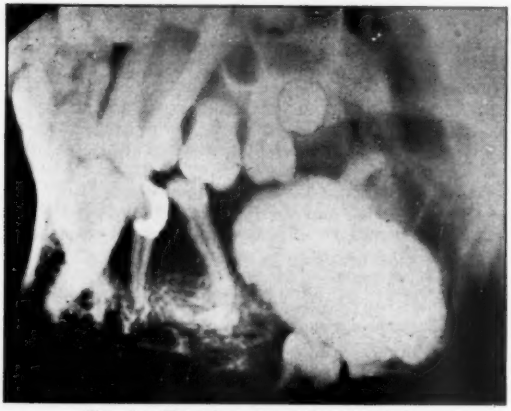


FIG. 1.—Complex composite odontome.

B. D., female, aged 18. Suppurating swelling in molar region of left mandible. Radiographs show circumscribed radiopacity at angle of mandible, with tooth at lower border (Fig. 1).

Abscess incised. Cap splints applied. Odontome and tooth removed by intra-oral approach. No fracture of mandible. Healed and splints removed twenty-eighth day.

*Pathology.*—Ovoid mass 1¾ in. by 1½ in. by 1 in. enclosing imperfectly formed tooth. Microscopical examination of decalcified specimen, chiefly dentine: Some spaces contain pulpal tissue, often with acute inflammatory infiltration; some spaces possibly had contained enamel.

**Peripheral Ivory Osteoma of Mandible.**—G. L. FORDYCE, F.D.S. R.C.S. (for RAINSFORD MOWLEM, F.R.C.S.).

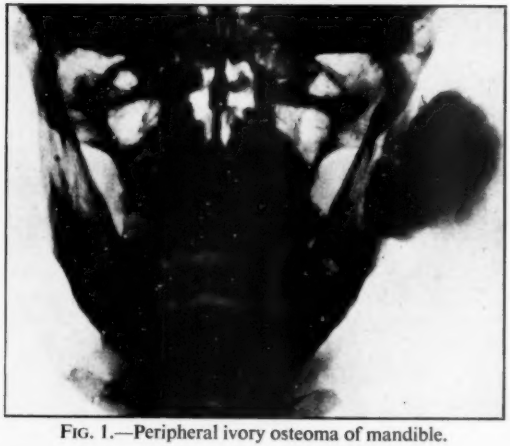


FIG. 1.—Peripheral ivory osteoma of mandible.

E. W., female, aged 68. Swelling of left mandibular ramus enlarging over twenty-five years. Painless, and mandibular excursion was normal. Bony hard on examination with irregular but well-defined margins. Facial nerve and parotid gland unaffected (checked by sialography). Radiographs demonstrate a lobulated radiopaque mass with evidence of a pedicle (Fig. 1).

Removed by a submandibular incision, together with the cortical bone surrounding the pedicle. Fracture of the condylar neck repaired with bone wiring. Uneventful convalescence.

*Pathology.*—Ovoid bony mass with convoluted surface 2 in. by 2 in. by 1½ in. The cut surface resembled ivory. Microscopical examination of decalcified specimen shows fully formed compact bone.

**Asymmetries of the Mandible.**—A. SHEFFORD, O.B.E., F.D.S. R.C.S., and W. B. BALDERSTON, L.R.C.P., L.R.C.S.Ed., L.D.S.

Photographs, radiographs and models were shown illustrating the following causes of asymmetry of the mandible:

(1) *Hyperplasia of one mandibular condyle.*—Two cases of this were shown; one showing gross asymmetry in a boy of 16, treated by condylectomy (Mr. D. N. Matthews) and the other a very slight asymmetry in a boy of 15½. This case had been observed for two years and the abnormal growth had apparently ceased.

(2) *Lack of condylar growth on one side.*—The case shown was a woman of 29 who gave no history of injury or disease and in whom asymmetry had been present since childhood. Radiographs revealed an absence of the glenoid fossa and gross malformation of the condylar head.

(3) *Permanent dislocation of one temporo-mandibular joint.*—This patient (Fig. 1) gave no history of injury, had a full range of movement of his mandible and was entirely free from symptoms. Radiographs revealed one condyle to be fully formed but dislocated forwards.

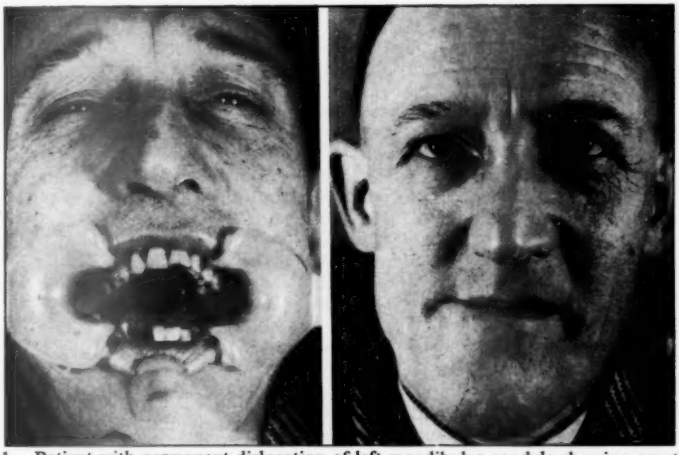


FIG. 1.—Patient with permanent dislocation of left mandibular condyle showing practically no limitation of movement.

(4) *Primary occlusal derangement.*—This patient had assumed a bite of convenience with her mandible deviated to the left and complained of pain in her temporo-mandibular joints. This deviation was due to premature loss of some posterior teeth and was corrected by bite rehabilitation which also cured her pain.

**Adamantinoma with Ulceration into Mouth.**—G. T. HANKEY, O.B.E., T.D., F.D.S., L.R.C.P., M.R.C.S., and J. A. PEDLER, M.D.S., F.D.S., L.R.C.P., M.R.C.S.

J. K., aged 78. *History.*—27.11.52: First seen with complaint of painful swelling of lower right gum, present for four months, with bleeding into the mouth for two months. Edentulous ten years. Existing full dentures fitted two years previously. *On examination.*—Swelling of body and ramus of right mandible. No attachment to skin. Fungating ulcer in the region of the lower right alveolar ridge and floor of mouth. It was hard, irregular and bleeding. *X-ray examination.*—A polycystic condition involving the body and ramus of the mandible with complete destruction of the superior border of the body. The region of the angle was not involved. *Diagnosis.*—Clinical diagnosis of adamantinoma was supported by report on biopsy taken from ulcer in mouth (9.12.52).

*Operation* 2.1.53 (Mr. Charles Donald).—Excision of right mandible (Fig. 1). Post-operative course uneventful.

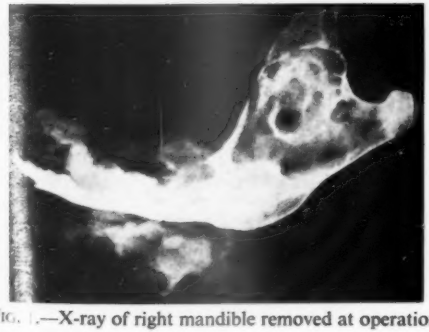


FIG. 1.—X-ray of right mandible removed at operation.

FIG. 2.—Photomicrograph (× 140) of typical field.

*Histopathology.*—Adamantinoma. Epithelial masses are bordered by columnar vacuolated cells with nuclei orientated away from the sparse connective tissue stroma. There are many small stromal cysts. Some larger cysts appear to have originated within the epithelial proliferations where in places the characteristic stellate reticulum appearance is seen (Fig. 2).

*Comment.*—The age of this patient is well above the average age of discovery of adamantinoma which was computed by Robinson (1937) from a series of 222 instances as being 30·1 years. In the same series, amounting to 379 cases in all, the highest age of discovery was 73.

It is also unusual for adamantinoma to present as an ulceration in the mouth. According to Thoma (1950) with the exception of a few atypical cases the soft tissues are not involved and he regards this as an important diagnostic point of differentiation from malignant tumours such as carcinoma. It is therefore of interest to record that in this case the patient was referred to hospital by his general practitioner as a case of carcinoma and that such a possibility remained until ruled out by the X-ray appearances and biopsy. Histological findings were typical of adamantinoma and had the added interest of presenting both epithelial cysts and some smaller stromal cysts as described by Lucas and Thackray (1952).

Excision of the right mandible has resulted in remarkably little deformity and speech is clear. In view of the patient's age no bone graft or plastic restoration is contemplated.

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**Chronic Lupus Erythematosus with Oral Manifestations.**—B. E. D. COOKE, F.D.S., M.R.C.S., L.R.C.P.

*Case I.*—Mr. M. A., aged 31 (Dr. L. Forman's case). *History.*—Recurrent ulceration of the left cheek for three years. Healed lupus erythematosus of nose, active lupus erythematosus of right pinna.

*On examination.*—Behind the right pinna there is a discoid scaly area 1 cm. diam. with an erythematous margin. Inside the left cheek (Fig. 1) anterior to Stenson's duct there is a depressed red granular area 1½ cm. by ½ cm. crossed with white lines and well demarcated from the surrounding mucosa. It is very firm on palpation.

←FIG. 1 (*Case I*).—Left cheek.

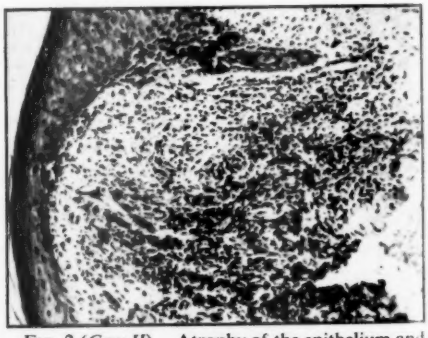

FIG. 2 (*Case II*).—Atrophy of the epithelium and lymphocytic infiltration of the middle and lower portions of the dermis. × 97.

*Histopathology.*—There is a dense lymphocytic infiltration of the lower portion of the dermis and there is only a sparse infiltration in the papillary layer. There are secondary changes in the epidermis leading to atrophy of the epithelial ridges, thinning and stretching of all the epithelial layers and a hyperkeratosis. Alternating with the atrophic areas there are areas showing acanthosis. The basal layer is incomplete and appears to have undergone a liquefaction degeneration.

*Case II.*—Mrs. J., aged 39 (Mr. R. D. Emslie's case). *History.*—Ten years' treatment for lupus erythematosus of the face, recent improvement with mepacrine.

*On examination.*—She has the typical batswing distribution of the erythematous lesion on the face. Gum: there is a localized erythematous lesion 0·3 cm. diam. on the attached gingivæ above $\underline{|12}$ which has remained the same in size and appearance to the patient's knowledge for four years. There are two more identical lesions on the gum over $\underline{|34}$ and $\underline{|5}$.

*Histopathology of the lesion over* $\underline{|12}$ (Fig. 2).—There are well-marked atrophic changes in the well-keratinized stratified squamous epithelium, with atrophy of the epithelial ridges and a thinning and stretching of all the epithelial layers. The vessels of the papillary layer of the dermis are dilated and there is only a sparse lymphocytic infiltration in contrast to the more dense lymphocytic and plasma-cell infiltration of the middle and lower portions of the dermis.

*Case III.*—Mrs. H., aged 38 (Professor W. E. Herbert's case). *History.*—Recurrent ulceration of the left cheek for four years.

*On examination.*—Left cheek: there is a sharply defined depressed area about 1 in. by $\frac{1}{2}$ in. opposite |8. The centre is slightly more red than the surrounding mucosa and has the appearance of epithelialized granulations. On palpation the centre has a slightly shotty feeling. Anterior to this lesion in the cheek there are two minute red areas, each with a smooth, lighter coloured centre. Right cheek: there is a symmetrically placed, smaller, almost identical lesion.

*Histopathology.*—Secondary atrophic changes of the dermis are not well marked but the vessels of the papillary layer of the dermis are dilated, and there is a sparse lymphocytic and plasma-cell infiltration. In the middle and lower portions of the dermis the infiltration is more dense with the lymphocytes and plasma cells forming clumps.

**Behcet's Disease.**—W. FRASER-MOODIE, L.R.C.P., L.R.C.S.Ed., F.D.S. R.C.S.

The first recorded case of the condition which now bears the name of Behcet was presented by Adamantiades to the Medical Society of Athens in 1930. Seven years later H. Behcet of Constantinople described what he believed to be a hitherto unrecognized clinical entity, in which there were associated oral, genital and ocular lesions.

Paintings, photographs and records of 4 cases of Behcet's disease were shown at the meeting. 3 were females and 1 a male.

Two of the patients were first referred to a dental out-patient department and one of these had suffered from ulcers of the mouth for four years and the other for over twelve years.

The genital lesions were troublesome in all cases. One woman developed a large deep ulcer of the vulva which increased within a few days of onset to about 2 in. by 1 in. and perforated the labia minora. The man had a recurrent epididymitis.

Eye lesions were present in 2 of the cases—1 had phlyctenules and the other iritis.

Numerous forms of treatment were tried. They included intravenous N.A.B., Antrypol, vitamins, antihistamines, various antibiotics and ACTH. While administration of ACTH produced initial healing of all lesions it is too early to assess final results.

**Primary Carcinoma of Lip. Arising from Sweat Gland.**—W. FRASER-MOODIE, L.R.C.P., L.R.C.S.Ed., F.D.S. R.C.S.

In April 1952 a schoolgirl, aged 15, presented with a small, painless, indurated mass in left upper lip.

Biopsy taken from the oral aspect of the lip: "... cellular elements of this tumour reminiscent of oat-cell carcinoma or any form of spindle-cell carcinoma. The units of cells are infiltrative between the bundles of connective tissue and muscle ... it would be difficult to come to a final decision especially as to a possible primary site elsewhere (bronchus, suprarenal, &c.) ..."

Commenced course of deep X-ray therapy at once.

Appeared to respond satisfactorily. Re-admitted 21.7.52 with glands palpable in the left submandibular and mid-cervical regions. Teleradium was applied to these metastatic areas.

Died 9.11.52. Cause of death given as carcinomatosis from primary carcinoma of sweat gland; multiple hæmorrhages and anæmia resulting from diffuse microscopic involvement of the bones. The immediate cause was anæmia with cerebral hæmorrhage.

**Non-neoplastic Destruction of Lower Lip.**—W. FRASER-MOODIE, L.R.C.P., L.R.C.S.Ed., F.D.S. R.C.S.

A young farmer from Dublin presented with loss of lower lip. Condition present for two years and had received no treatment.

On examination the greater part of the lower lip was missing. The lower incisors and the gum were uncovered. The edge had some scar tissue, heaped granulations and a few deep fissures. Several sections taken for biopsy showed chronic fibrosis, inflammation but no evidence of malignancy.

Eventually the patient admitted having used a caustic stick on the lip daily for over two years, in an endeavour to cure some cracks on the lip.

A plastic operation was performed to restore a lower lip and he returned to his farm.

Six months later he reported for follow-up. The appearance was excellent and the function good.

**Palatal Root Resection in a Diabetic.**—W. G. Cross, M.B., M.S., B.D.S.

*History.*—Mr. G. A., aged 37, a diabetic receiving 60–80 units of zinc protamine insulin daily, was referred by own dentist on account of pain and periodontal disease in $\underline{|6}$. Pus had been drained away by placing a probe down the periodontal membrane.

*Examination.*—A well-kept mouth. $\underline{|6}$ was heavily filled, non-vital, and exhibited slight mobility. A 12 mm. pocket was present palatally, from which some pus could be expressed.

X-rays showed the tooth to be root filled in all three canals, and bone resorption to be present around the palatal root (Fig. 1).

*Treatment.*—The case was considered ideal for root resection—palatal root involved, the tooth dead and root-filled, and necessary for function. Under a limited amount of Xylocaine (2%, adrenaline 1 : 80,000) the gum was resected palatally and the root resected with a fissure burr. The cut surface was then smoothed, and a cement pack inserted.

The case was shown ten days post-operatively. Subsequent healing has been entirely uneventful; the tooth is as firm as before the operation. X-rays taken one week post-operatively are shown in Fig. 2.

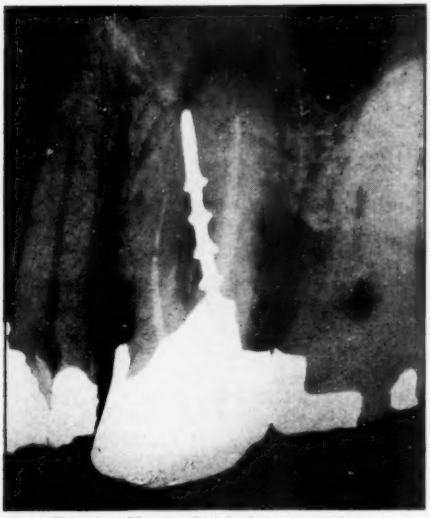

Fig. 1.—X-ray of $\underline{|6}$ before operation.

Fig. 2.—X-ray of $\underline{|6}$ one week after operation.

**Squamous Carcinoma of Mandible.**—J. H. Hovell, F.D.S., L.R.C.P., M.R.C.S.

G. H., male, aged 49.

14.6.49: Patient presented with papillomatous tumour in $\overline{|78}$ region. Clinical appearance of fibrous epulis but with rapid growth (three months' duration). Bleeds easily and slightly friable.

Biopsy report: Early carcinomatous change.

28.6.49: $\frac{|5678}{|56}$ removed and impression taken for radium applicator. Radiotherapy instituted.

6.4.50: Radiographic evidence of small area of radium necrosis in region of $\overline{|6}$. Advised to wait for separation. Attended several times between 4.7.50 and 12.12.50.

25.9.52: Radionecrotic area has now reached lower border of mandible. Advised resection and bone graft. Cap splints constructed.

9.10.52: Admitted for resection of left body of mandible including necrosis. No evidence of recurrence of carcinoma.

10.10.52: *Operation.*—Cap splints fitted followed by: (1) Extraction of $\overline{|4}$. (2) External incision along lower border of left mandible. (3) Left mandible removed from $\overline{|3}$ region to level of inferior dental foramen. (4) Intermaxillary fixation. Satisfactory recovery except for development of a small area of bone necrosis in $\overline{|3}$ region which necessitated the removal of this tooth with the surrounding alveolar bone under nitrous oxide anæsthesia.

26.11.52: Readmitted for bone graft. *Operation.*—Bone graft from iliac crest. Inserted and wired into position. Intermaxillary fixation.
6.1.53: Satisfactory recovery.
The patient is now back at work with a fully functional mandible.

**Carcinoma of Submaxillary Gland.**—J. H. HOVELL, F.D.S., L.R.C.P., M.R.C.S.

F. M., male, aged 71. Referred with swelling in right submandibular region. The tumour was approximately 2 in. in diameter with irregular edge, slightly tender. Attached to skin and floor of mouth. No ulceration in the mouth.

X-rays show area of bone erosion in right body of mandible, most extensive in $\overline{6}|$ region.
Biopsy showed evidence of squamous-cell carcinoma, little differentiation, plentiful mitosis, Grade II.
Investigation revealed no primary elsewhere.
Diagnosis: Primary carcinoma of right submaxillary gland.
Owing to the close proximity of the tumour to the mandible, a combination of radiotherapy and surgical treatment was advised.
4.8.52: Admitted for the extraction of all teeth.
14.8.52–14.10.52: Full course of radiotherapy instituted.
23.10.52: Resection of right mandible and removal of submaxillary salivary and lymphatic glands.
16.1.53 : Wound healed. No clinical sign of recurrence.
*Pathological report.*—No definite carcinomatous cells seen, only degenerating epithelial cells surrounded by much fibrosis.
Owing to patient's age, it is not intended to replace the mandible with a bone graft.

**Maxillary Osteotomy and Tube-pedicle Repair of Palatal Fistula.** — Mr. PATRICK CLARKSON and Mr. W. GROSSMAN showed a film of the late repair of cleft palates by combined maxillary osteotomy and tube-pedicle closure of the palatal fistula whereby the collapsed maxillary alveolar arch was reduced and the speech improved by repair and elongation of the soft palate by tube-pedicle tissues.

[*April* 27, 1953]

## Spindle-cell Sarcoma in the Black Leopard (*Panthera Pardus*)

By RUDOLPH SPRINZ, F.D.S. R.C.S.
(*From the Department of Anatomy, Royal College of Surgeons of England*)

THE Black Leopard, "Satan", was killed on November 14, 1952, and a post-mortem examination was made the following day. The animal was emaciated, having been ill for some time.

The post-mortem showed a localized condition involving the right upper and lower jaws. Of the upper jaw, the jugal and the posterior aspects of the maxillary bones were destroyed, the pterygoid region being filled with a large necrotic mass. The middle cranial fossa was not involved.

The lower jaw was expanded by a soft new growth which had eroded the outer plate of bone, presenting an irregular nodular swelling. The coronoid process (which is large in carnivora giving attachment to the temporalis), the condyle as well as the posterior third of the horizontal ramus of the jaw were replaced by the tumour mass. The lesion was of a firm consistency but presented a number of cystic spaces (Fig. 1). An X-ray of the jaw (Fig. 2) showed a large radiolucent area extending from the anterior root of the 2nd premolar tooth to the condyle of the jaw (one retained root of the 1st premolar could be seen just anterior to the mental foramen). The area presented cystic cavities of varying size and the inferior margin of the lesion showed an irregular (eroded) outline. The roots of the carnassial tooth (1st molar) were completely resorbed and the posterior root of the 2nd premolar also showed resorption. Two pathological fractures could be noted, one at the lower border of the jaw, below the carnassial tooth, and the other between the horizontal ramus and the condylar process. The latter fracture caused the condyle to be pressed downwards so as to lie on a level with the lower border of the jaw.

One of the outlying groups of the submaxillary lymph glands was enlarged, though not attached to the deep tissues. Bisection of the gland showed that it had been replaced by tumour tissue following metastatic spread.

The carnassial tooth as well as the premolar teeth on the left side were fairly clean. Thick dark calculus was deposited on the teeth of the right side. This was particularly so in the case of the mandibular 2nd premolar and the carnassial tooth. This latter tooth was loose, its roots having been completely eroded by the tumour. A few strands of fibrous tissue were all that held the crown in place.

Histological preparations of the lesion were made on which Dr. L. W. Proger of the Pathology Department of the Royal College of Surgeons reported:

*Gland:* The tumour is composed of interlacing bundles of spindle cell with little intercellular material. Regimentation of the nuclei in places suggests a possible neurogenic origin (Figs. 3 and 4).

FIG. 1.—Right side displaying a cystic cavity.

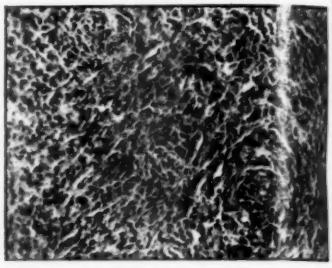

FIG. 3.—Tumour tissue from submandibular lymph gland × 50.

FIG. 2.—X-ray of right side showing radiolucent area and the two pathological fractures.

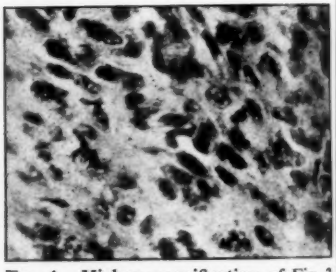

FIG. 4.—Higher magnification of Fig. 3 × 150.

*Jaw:* Section of the lesion itself was indicative of the same tissue, the superimposed infective process somewhat masking the histological picture of the condition. In no portion of the tumour was any osteoblastic activity observed.

*Discussion.*—The massive destruction of the jaw, the calcareous deposits on the teeth and the resorption of the roots of the teeth indicate that the tumour had been present for some time. The fact, however, that the lymph gland showed considerable growth of metastatic deposits suggests that the tumour had been relatively benign until recently, when there was a sudden dissemination of sarcoma cells into the lymph stream.

In man this type of tumour is rare. Geschickter and Copland (1949) give to such a lesion the name of "osteogenic osteolytic sarcoma". These authors suggest that in man its common positions are: upper end of humerus, lower end of femur, upper end of tibia, though it is uncommon in the jaws. They stress that in older people this tumour can follow a protracted course. Histories of up to four years are recorded, but most patients come under treatment one year after onset of symptoms. The radiographic appearance does frequently present a picture very like that of benign giant-cell tumour. The sarcoma, however, shows an unusual tendency to produce spontaneous fractures, and lymphatic involvement is not uncommon.

As the condyle of the jaw as well as the glenoid fossa were involved in the destructive process, the pathological fractures of the jaw made it possible for the animal to perform a limited amount of jaw movement.

It is suggested that this animal was suffering from this lesion and the superimposed infection for at least six months, possibly much longer. It is fairly certain that this animal would not gladly have submitted itself to a detailed dental inspection; it was indeed known for its wild nature.

Acknowledgment is made to the Zoological Society of London for this specimen.

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# Section of Pædiatrics

President—D. W. WINNICOTT, M.A., F.R.C.P., M.R.C.S.

[*March* 27, 1953]

## DISCUSSION ON SOME PROBLEMS OF PREMATURITY

**Professor D. Baird:**

### *The Prevention of Prematurity*

By international agreement a premature baby is defined as one weighing 5½ lb. (2,500 grammes) or less at birth. The term "prematurity" is therefore misleading, as the length of gestation does not enter into the definition. It follows that prematurity—as defined—can arise either from premature termination of pregnancy, by accident or design, or from impaired fœtal growth, resulting in an underweight baby at or near term. From the point of view of prevention, two things are necessary: (*a*) adequate fœtal growth; (*b*) continuation of pregnancy until the fœtus is physiologically mature, irrespective of its birth weight.

Reports of the Registrar-General have shown that as social status declines the infant mortality from prematurity rises. This suggests that a study of prematurity at different social levels would be informative.

The following figures are from a comparison between all married primiparæ (excluding cases of twin pregnancy) confined (*a*) in a private nursing home in Aberdeen during the five years 1946–50, and (*b*) in the Aberdeen Maternity Hospital during the three years 1948–50. The nursing home cases came mainly from Social Classes I and II and the hospital cases from Classes III, IV and V. The incidence of live-born premature babies was 7·6 and 4·8% in the hospital and nursing home groups respectively. Table I shows that there were 25 deaths out of 204 premature babies (12·3%) in the

TABLE I.—PREMATURE INFANTS DISTRIBUTED BY BIRTH WEIGHT

*Booked Legitimate First Births (Excluding Twins)*

| | Maternity hospital group 1948–50 | | | Private nursing home 1946–50 | | |
|---|---|---|---|---|---|---|
| Total births | 2,686 | | | 1,025 | | |
| Live-born "prematures" | 204 | (7·6%) | | 49 | (4·8%) | |
| Birth weight | Died | Lived | Total | Died | Lived | Total |
| Under 3 lb. .. | 6 | 3 | 9 | — | — | — |
| 3–4 lb. .. .. | 13 | 14 | 27 | — | 3 | 3 |
| 4–5 lb. .. .. | 6 | 59 | 65 | 1 | 14 | 15 |
| 5–5½ lb. .. .. | — | 103 | 103 | — | 31 | 31 |
| All weights .. | 25 | 179 | 204 | 1 | 48 | 49 |

hospital group and 1 out of 49 (2·0%) in the nursing home group. In the hospital group there were 36 babies of 4 lb. or less (18% of the total) and they contributed 75% of the deaths. In the nursing home group only 3 out of 49 babies (6%) were 4 lb. or less and none of these died. One reason for the excess mortality in the hospital cases is the greater number of very small babies.

*Circumstances of prematurity.*—Table II shows that the incidence of "premature" babies born after 38 weeks' gestation or longer was the same in each group—3·6% of the total births, but the incidence of gestation of less than 38 weeks was more than three times as great in the hospital as in the nursing home group. This greater incidence of premature onset of labour was seen in the cases where the pregnancy seemed "normal" as well as in those where a recognized abnormality of pregnancy or the fœtus was present.

The most common abnormality of pregnancy requiring induction was pre-eclampsia and the most common cause of spontaneous onset of premature labour, accidental hæmorrhage without pre-eclampsia.

*Consequences of prematurity.*—Table II shows that 77% of the nursing home and 38% of the hospital premature babies required no special treatment. The mortality from prematurity per 1,000 live births was 1 and 9 in the nursing home and hospital groups respectively so that it is evident that the overall prematurity rates of 4·8 and 7·6% do not bring out fully the great differences between the groups.

TABLE II.—BOOKED LEGITIMATE FIRST BIRTHS (EXCLUDING TWINS)

| *Circumstances of Prematurity* | Maternity hospital Gestation period | | Private nursing home Gestation period | |
|---|---|---|---|---|
| | 37 wks. or less | 38 wks. or more | 37 wks. or less | 38 wks. or more |
| Labour induced for abnormality of pregnancy | 15 (0·6) | 7 (0·3) | 1 (0·1) | 3 (0·3) |
| Spontaneous onset of labour associated with abnormality of pregnancy or fœtus | 29 (1·1) | 19 (0·7) | 3 (0·3) | — (0·0) |
| Spontaneous onset of labour following normal pregnancy | 63 (2·3) | 71 (2·6) | 8 (0·8) | 34 (3·3) |
| Total "Prematures" | 107 (4·0) | 97 (3·6) | 12 (1·2) | 37 (3·6) |
| *Consequences of Prematurity* | | | | |
| Neonatal death | 25 (12·3%) | | 1 (2·0%) | |
| Prematures surviving after at least fourteen days in Special Nursery | 101 (49·5%) | | 10 (20·4%) | |
| "Normal" prematures | 78 (38·2%) | | 38 (77·6%) | |
| Total "Prematures" | 204 (100·0%) | | 49 (100·0%) | |

The figures inside the brackets denote per cent.

*Prevention.*—The hospital cases were under the care of specialists throughout. They attended the antenatal clinic of a teaching hospital and were delivered in the hospital. The city is well supplied with beds for the treatment of antenatal complications so that the patients were admitted for as long as was thought necessary to treat adequately such conditions as pre-eclampsia, anæmia and debility, and antepartum hæmorrhage. After delivery the babies were under the care of the Professor of Child Health and his staff in a nursery specially equipped to deal with the problems of prematurity. The nursing home patients were mostly under the care of the family doctor during pregnancy and labour and, as no similar facilities were available in the nursing home, mothers or babies requiring special treatment were transferred to hospital. For statistical purposes such cases were included in the nursing home group, even when the labour took place in hospital.

The high incidence of prematurity, therefore, occurs in the hospital group despite a very high standard of antenatal care. In fact in 65% of cases where the baby was 5½ lb. or less at birth and in 59% of cases where labour began before the 38th week, pregnancy was judged to be normal. This confirms the fact that something more than very good routine antenatal care is necessary to prevent such cases. The fact that so many small babies died despite expert obstetric and pædiatric treatment in the hospital and so few in the nursing home series suggests that prevention of prematurity offers more scope for lowering mortality than further improvements in the treatment of very premature babies. Treatment has improved so much in recent years that in the most efficient nurseries only those babies whose tissues are too immature for independent existence die. The survival of large numbers of very small infants may be producing new problems, such as retrolental fibroplasia.

The contrast in different social groups brought out in the above analysis suggests that improvements in the general standard of living would decrease the incidence of prematurity still further. There is a good deal of direct evidence to support this. For example, the fall in the death-rate from prematurity was accelerated throughout Britain in the years 1942–44 due probably to improved diet of pregnant women at that time brought about by full employment and the national wartime food policy. Further improvements in diet during pregnancy would probably decrease the prematurity rate still more. The giving of advice on diet should therefore be an important function of antenatal care. Too much cannot be expected, however, since it is difficult to influence the food habits of most adults. In addition the quality and quantity of food intake during pregnancy is only one of the factors influencing the outcome. The nursing home group is superior in health and physique and, as I have shown in a previous publication (Baird, 1952), this influences greatly the prematurity rate. This superior health is the result of a better diet and healthier living conditions from birth to maturity. A very low prematurity rate must await the attainment of a much higher national standard of living, and this is a very long-term policy dependent on world-wide factors mostly beyond our immediate control. In the meantime we must try to minimize the deleterious effect of our relatively high rate of prematurity by maintaining the best possible standard of obstetrics and pædiatrics.

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**Professor W. C. W. Nixon** presented data collected from the Premature Baby Unit of University College Obstetric Hospital. There were 175 cases of premature births during the years 1951–52, and an analysis of these showed the following causes—pregnancy toxæmia 23·5%, multiple pregnancy 15·5%, antepartum hæmorrhage 9·0%, unknown (including spontaneous rupture of membranes) 37·7%, miscellaneous 14·3%. It was the group of "unknown" causes that needed further investigation, and Professor Dugald Baird had already shown that social factors might be responsible.

The obstetrician should be able to reduce the incidence of premature delivery due to antepartum hæmorrhage, particularly that due to placenta prævia. Such cases should be admitted to hospital. By conservative treatment the gestation could be coaxed to greater maturity and the pædiatricians presented with a more vigorous baby.

Weight control by dietetic restriction in pregnancy might reduce the incidence of pregnancy toxæmia. In Sydney strict supervision of the pregnant woman in this way had almost eliminated the problem of prematurity due to pre-eclampsia.

**Professor J. C. McClure Browne:**

*The Causation of Prematurity*

In the causation of prematurity, Dr. V. M. Crosse has shown that pre-eclamptic toxæmia accounts for 16%, accidental hæmorrhage 6·5% (and this is largely toxæmic in origin) and twins 11%—a total of 33%.

There is another cause—premature rupture of the membranes—which occurred in 7% in a survey which I carried out four years ago. Thus pre-eclamptic toxæmia, accidental hæmorrhage, twins and premature rupture of the membranes account for 40% of these cases. Now, if we could eliminate prematurity from these causes, the problem of prematurity would be nearly half-way to solution.

*First, pre-eclamptic toxæmia* is not a condition arising as a result of disturbance in the placenta, but is closely bound up with the functioning of the adrenal cortex in its role as master of water, salt and potassium distribution in the body. This function may be conditioned by many factors—diet, ACTH, and anterior pituitary disturbances generally. For years we have concentrated on the placenta, and have failed to look further afield. With the idea that the adrenal cortex held the key, Carey has used the exchange resins to extract water from the body, so that it is now possible to hold the condition in check for a month or more; meanwhile the baby grows. I would, however, plead that in minimal antepartum hæmorrhage the employment of expectant treatment be more widely used; this means more antenatal beds.

*Secondly, twins.*—Here all our efforts should be directed to prolonging pregnancy. I admit all cases of twins from the 32nd week, because rest in bed is still our most potent therapeutic weapon. The use of progesterone, suggested by Snyder's experiment in 1934, has proved utterly disappointing.

*Thirdly, premature rupture of the membranes.*—Several years ago, I surveyed the incidence of premature rupture of the membranes as a cause of prematurity, and found it to be present in 7% of cases. Experiments showed that the pressure needed to rupture the membranes depended on the size of the os. If the os was undilated, a pressure of 120 mm.Hg was needed. If the os was fully dilated, a pressure of only 30 mm.Hg was needed. Another factor, which did not apply before 38 weeks, was the size and fit of the presenting part. Recordings of uterine contractions from 32 weeks onwards showed occasional powerful painless contractions exerting a pressure of the order of 100 mm.Hg, i.e. more than the normal Braxton Hicks contractions. It may well be that these contractions could on occasion cause premature rupture of the membranes and consequent prematurity. We need more studies of the pattern of uterine contractions in pregnancy, and of the effects of drugs on these.

CONCLUSION

If we can control pre-eclamptic toxæmia (and therefore accidental hæmorrhage), if we can prolong twin pregnancy, and if we can quieten the active uterus in late pregnancy, prematurity would be reduced by nearly half.

**Dr. R. H. J. Hamlin:** During the years 1946–51 at the Women's Hospital, Sydney, the incidence of pre-eclamptic albuminuria fell from 10% (418 cases) in 1946 to 1·8% (84 cases) in 1951 (Hamlin, 1953).

The new antenatal care employed in the years 1948 to 1951 (diet instruction and weight control) had so reduced the prevalence and severity of pre-eclampsia that, during the final eighteen months of this period, induction of labour between the 30th and 37th weeks of pregnancy was rarely performed, and Cæsarean section, for this indication, was not employed at all. I am therefore convinced that the number of babies born prematurely because of pre-eclampsia can be greatly lowered by an attack on this maternal disease.

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**Dr. H. M. M. Mackay:**

*Complications of Prematurity*

The main object of the pædiatrician in charge of premature babies is first to prevent death and secondly to promote health. In J. E. Morrison's series of post-mortem examinations on premature infants, 50% to 80% of the neonatal deaths in his different birth-weight groups were due to anoxia secondary to causes outside the infant. The treatment of these anoxic or asphyxiated infants varies widely, and a satisfactory controlled comparison of different methods of resuscitation is all but impossible. But as a good overall survival rate for small premature infants presumably indicates reasonably good methods of treatment, such rates should always be given by those advocating particular methods of resuscitation. Even so, one must remember that very large numbers are necessary for firm conclusions to be drawn. For example, at the Mothers' Hospital over 10,000 infants, including nearly 600 premature infants, have been born alive in the past five years; the overall premature neonatal mortality rate has been 13% of premature live births, but it has fluctuated in different years from 5% to as much as 17%. Our methods of resuscitation are somewhat inactive, but at present I know of no evidence proving that more active methods bring about a higher survival rate.

Can anyone present help with such problems as these: What are the best methods of clearing air passages? Has anyone a really satisfactory mucus catheter with bulb suction? Is there a really satisfactory plastic fabric oxygen tent for premature infants?

Personally, I stress the need of maintaining the body temperature between 98 and 99° F., if possible, as a low temperature means a lowered vitality. If infants infected before or during birth are to be saved, prophylactic treatment with antibiotics must be started at the earliest possible moment. Every chilled infant and every infant thought to have aspirated fluid requires antibiotic treatment—a point of great importance. The co-operation of obstetricians would be valuable in giving antibiotic treatment much more readily to the mother, thus providing an umbrella for the infant likely to be exposed to infection before birth.

If we are to increase our knowledge of the complications of prematurity—whether these be kernicterus, retrolental fibroplasia, susceptibility to infection, or early anæmia—it is important that premature babies be followed up by the pædiatric staff of the maternity department. The divorce of this work from the hospitals would be disastrous to the interests of premature babies.

**Dr. A. White Franklin:**

*Mortality in Prematurity*

The study of death-rates and the causes of death in premature and immature babies raises many difficult problems. The figures from the Queen Charlotte's Maternity Hospital Annual Reports show that in the period 1948–1951 of 133 neonatal premature deaths only 33 occurred after the first forty-eight hours, an average of about 8 cases a year (Table I). The bulk of the problem is thus

TABLE I.—PREMATURE BABIES 1948–1951

| | | Mortality | | |
|---|---|---|---|---|
| | | Weight | Total | Died | Per cent |
| Total liveborn .. .. .. | 11,391 | | | | |
| Total stillborn .. .. .. | 303 | 2½ lb. and less | 50 | 38 | 76 |
| Liveborn prem. .. .. .. | 748 | 3½–2½ | 72 | 32 | 44 |
| Stillborn prem. .. .. .. | 172 | 4½–3½ | 172 | 38 | 22 |
| Prem. neonatal death .. .. | 133 | 5½–4½ | 445 | 18 | 4 |
| Death within 48 hours .. .. | 100 | unknown | 9 | 7 | — |
| Death after 48 hours .. .. | 33 | | | | |

referred to intra-uterine disease, or intrapartum injury or failure, and drives the pædiatrician who wishes to try to influence events into the antenatal clinic and the labour ward.

An analysis of morbid anatomical findings shows the great frequency of lung lesions which were present in 83% of cases in one series studied. They appear as the cause of death in 56 of the 98 cases where a diagnosis was possible in the premature group reported here (Table II). Of the

TABLE II.—POST-MORTEM CAUSE OF DEATH

| Surviving 48 hours | | Total |
|---|---|---|
| 7 | Hæmolytic disease .. .. .. .. .. .. | 13 |
| 2 | Congenital anomaly .. .. .. .. .. .. | 8 |
| 2 | Intracranial hæmorrhage .. .. .. .. .. | 18 |
| 3 | Pulmonary hæmorrhage .. .. .. .. .. | 7 |
| 3 | Extra-pulmonary infection .. .. .. .. .. | 3 |
| 6 | Unknown .. .. .. .. .. .. .. | 35 |
| 9 | Pneumonia .. .. .. .. .. .. | 16 (none 1951) |
| 1 | Other lung lesions .. .. .. .. .. .. | 33 |

treatable causes of death in prematures surviving forty-eight hours hæmolytic disease and pneumonia were the two important ones. From 1951 antibiotics were much more readily used as a routine treatment for newborn babies born after prolonged labour, or when there was any appreciable aspiration of liquor. In these cases injections of streptomycin (20 mg. per lb. per day) and penicillin (100,000 units b.d.) were given for three days at least. This has been followed by a marked drop in deaths from pneumonia but the experience is too short and too small to be more than suggestive.

To the question "What is the cause of death?" some pathologists suggest an answer, others leave the matter in doubt. The difficulty is to pick the cause of death out of the effects of dying. And if he finds that the cause is a hyaline membrane, is the pathologist right, or is the mother, who says "I lost my baby because I fell out of bed"? To correlate the whole story of the pregnancy and the confinement and the events leading up to the baby's death with post-mortem results is very difficult, and to discover when and why the trouble really arose needs a full case conference of all concerned, including obstetrician, pædiatrician, pathologist and almoner.

**Dr. B. W. Powell:**

*The Effects of Environment*

Since the pioneer work of Blackfan and Yaglou it is surprising how little attention has been paid to the physical conditions to which premature babies are subjected. Certain standards were laid down by these and other workers and have been very little altered during the last twenty years.

Recent work has suggested that a relatively high humidity may be helpful in some cases of respiratory distress, but this requires further investigation.

With regard to temperature, during the winter months it is not uncommon for babies to be admitted from the district with a rectal temperature well below 90° F.; this fall occurs immediately after birth and usually improves during the ambulance journey to hospital. In these cases it is important to warm the baby up with care and not to subject him to too sudden a rise in temperature. Although some babies tolerate this extreme of temperature well, in many it gives a poor prognosis.

Attention has also been drawn recently to the importance of oxygen and the possible dangers of too high a concentration in the air which the baby breathes. Experience has shown that with the apparatus and flowmeters commonly used, very high concentrations of oxygen can build up without being suspected. A routine check on this, using a simple method of oxygen sampling, is very desirable. At the Premature Baby Unit at Hammersmith this is now done three-hourly by the nursing staff, and forms a valuable check, but it matters little what the oxygen concentration may be if the baby is unable to make it available to the tissues. At Hammersmith we have been gaining experience with methods evolved by Mr. Ian Donald of assisting the babies' respiratory efforts.

**Dr. N. R. Butler:**

*Environmental Conditions in Prematurity*

The question of what constitutes the optimum physical environment for premature infants is still a battleground of opinion, largely unsupported by scientific evidence. An attempt has been made in Table I to summarize previous work and to recommend suitable conditions of temperature, humidity and oxygen control in the light of present knowledge.

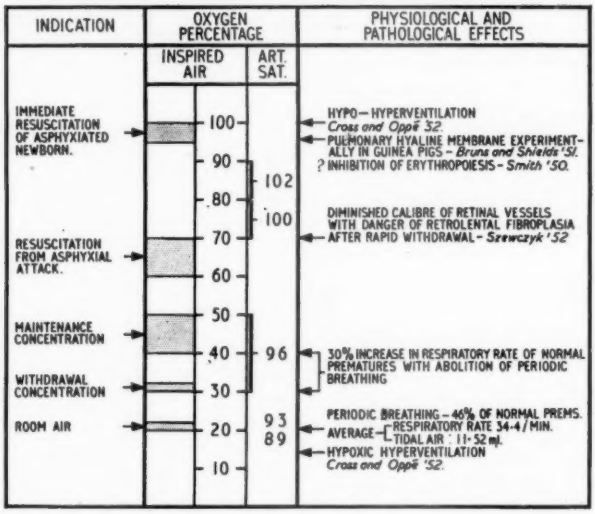
Nearly all premature infants who weigh over 1,750 grammes have a mature heat-regulating centre and sweating mechanism, and do not need to be nursed in a specially controlled environment. It has been shown in this group that weight gain and growth are maintained better in 30% than in 60% humidity (Blackfan and Yaglou, 1933). For the smaller premature infant, the majority of clinical opinion upholds the superiority of a warm, humid and adequately ventilated atmosphere. The twenty-year-old concept of control of environmental temperature at 75° to 85° F. and a humidity of 65% still holds as the basis of modern treatment. A more recent innovation is the nursing of small premature infants without clothing at 90° F., in order to facilitate respiratory movement and to allow constant observation. Such treatment must be carried out in an incubator or special hot room.

*Humidity.*—While 30% humidity has been found by the same authors to interfere with the growth and digestion of small premature infants, a high environmental humidity of 90% to 95% has been advocated (Potter, 1952) as possibly advantageous in respiratory difficulties for the prophylaxis of hyaline-like membrane. Various wetting agents and mists have also been advocated for the condition, and the potential danger of high oxygen concentrations has been stressed by the experimental production of hyaline-like membrane in guinea-pigs (Bruns and Shields, 1951). As this condition occurs both in prematurity and after Cæsarean section it would appear reasonable to nurse all premature infants delivered by this route in high humidity (95%) whenever practicable for the first two or three days after birth.

*Oxygen.*—There is an increasing volume of experimental evidence stressing the potential toxicity of high oxygen concentrations to vascular endothelium particularly in the retina and lung. The mechanism may be partly that of interference with enzyme action on pyruvate oxidase, as in brain

TABLE I

OXYGEN CONCENTRATION FOR PREMATURE INFANTS




tissue poisoned with oxygen (Dickens, 1946). Inhibition of erythropoiesis may also be a danger (Smith, 1950). The original recommendation for premature babies was 40% oxygen (Hess *et al.*, 1934) and this level has also stood the test of time although, in the light of possible toxicity, oxygen should never be administered as a routine measure, being reserved for those cases with a definite indication such as cyanosis or respiratory difficulty. The normal premature under 1,500 grammes suffers from only a 6% reduction in arterial oxygen saturation compared with the normal adult saturation of 95%, and this small deficit is made good in 40% oxygen, which also abolishes periodic respiration (Graham *et al.*, 1950). Szewczyk (1952) believes that the former practice of keeping premature infants in uncontrolled oxygen concentrations at or above 60% with sudden rather than graduated withdrawal to room atmosphere is responsible for retrolental fibroplasia. It is therefore imperative that when oxygen has to be administered for prolonged periods the concentration should be controlled at a level not higher than 50% with a period at 30% during withdrawal.

In those oxygen boxes which encompass the whole infant, such as the Queen Charlotte's type, separate individual calibration is necessary for each baby in view of the inevitable variation in leakage rate. This may result in a fluctuation of 36–80% at a flow of 2 litres per minute in different boxes (Gunn *et al.*, 1952). This may entail several readings before the correct concentration is achieved and the basal level may again be altered during treatment if any manipulation of the apparatus is necessary. Therefore, a more efficiently controllable method of oxygen administration would appear to be with a cot of Sorrento type with metal sides and transparent plastic or Perspex close-fitting lid, containing a minimal ventilation hole such as $\frac{3}{8}$ in. diameter. Provided an accurate flowmeter is employed, no further individual calibration is required. The Sorrento type, as above, which has a volume of approximately 93 litres, gave in six similar cots so tested an oxygen concentration of 46–50% maintained steadily when tested at two-minute intervals over a two-hour period, using an initial oxygen flow of 8 litres per minute for the first two minutes, followed by an economical maintenance rate of $\frac{1}{2}$ litre per minute. The cot contained an average-size mattress and the readings were found to be independent of the weight of the baby throughout the range tested of 1,250–2,500 grammes. The $CO_2$ concentration did not rise above 0·36% when sampled 2 in. from the mouth of the baby after one and a half hours. Cross and Oppé (1952) confirm that the respiratory centre of premature infants is not unduly sensitive to such a concentration of $CO_2$ in inspired air. For the actual estimation of oxygen concentration the simple chemical pyrogallol method (Pirnie and Allchorne, 1952) was found to be accurate to within 2%, compared with the expensive electromagnetic method or the laborious Haldane gas-analysis.

*Incubators.*—There is no doubt that under the different circumstances discussed above it may be necessary to alter independently the environmental temperature, humidity and oxygen concentration, for which no better method exists than the air-conditioned incubator. The type fitted with sleeves has the advantage of avoiding fluctuations when attention is required for the infant. These special

environmental needs are a further indication for the transfer from home of all but the most robust small premature infants weighing under 2,000 grammes to specially equipped centres as soon as possible after birth.

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**Dr. Trevor P. Mann:** There is a tendency nowadays to overheat premature infants. Dr. Helen Mackay had said that in her Unit they considered a rectal temperature of 98–99° F. desirable. This surely is too high. A small premature infant nursed in a room with a temperature of 70–75° F. usually stabilizes his body temperature at about 97° F., that is, at a relatively lower level than that achieved in similar circumstances by the average full-term baby. If an optimum rectal temperature must be fixed then one of 97° F. rather than 98–99° F. would probably be safer and less liable to lead to cyanotic attacks.

During the winter we were familiar with the small premature infant who was brought into hospital at the age of a few days in a refrigerated state, with a rectal temperature of perhaps 86–90° F. On admission the baby was usually an impressive pink colour and often did not look ill. In the past our efforts had been directed, in the first instance, towards warming these infants. As their temperatures were pushed up, and incidentally their oxygen requirements increased, some of them became ill and developed cyanosis, even in an oxygen box. The mortality rate was high with such treatment and at post-mortem an infection, often a pneumonia, was found which had not been detected clinically. Recent limited clinical experience at the Royal Alexandra Hospital for Sick Children, Brighton, suggested that this type of case stood a better chance if kept cool for a few days. Antibiotics had been given as a routine to deal with an occult infection.

**Dr. R. E. Bonham-Carter:** Dr. Mann's observation is correct; if a baby is chilled the oxygen demand of the tissues drops, and if warmed up quickly it is possible that this demand will increase beyond the supply, if respiration is impaired, and the baby will become anoxic. It is possible that the rate of warming up should be gradual if this is to be avoided.

**Dr. V. Mary Crosse:**

*Subsequent Development of Premature Babies*

It is necessary to consider physical, mental and emotional development.

Certain factors are known to influence subsequent development:

(1) *Degree of prematurity*: When assessing development an allowance must always be made for the degree of prematurity; development starts from conception and not from birth.

(2) *Fœtal abnormality*: In Birmingham no less than 25% of all babies with fœtal abnormalities are born with a birth weight below 5½ lb.

(3) *Increased liability of premature babies to certain neo-natal conditions, i.e. birth injury, kernicterus and retrolental fibroplasia*: Kunstadter of Chicago traced 69 premature infants who had survived intracranial birth injury: 39% showed damage to the central nervous system (hydrocephalus, increased deep reflexes and definite spasticity), and 19% showed mental retardation.

The premature baby is more liable to suffer from kernicterus due to Rh iso-immunization, and also kernicterus of prematurity (not associated with the rhesus factor) and one must therefore expect more spasticity, athetosis, deafness, and mental retardation in these infants.

Premature babies are also more prone to develop retrolental fibroplasia and blindness.

(4) *Birth weight*: The incidence of both fœtal abnormality and birth injury increases as the birth weight decreases. Subsequent development is therefore more likely to be abnormal in the smaller premature babies.

These factors sound depressing, but must be faced. In any case some of these complications can be avoided if their possibility is recognized, e.g. birth injury and retrolental fibroplasia.

Fortunately, there is a more cheerful side to the picture. It is generally recognized that if a premature baby is born without fœtal abnormality, and escapes the complications already men-

tioned, then it has every chance of developing as well as a larger baby, but at any particular stage an allowance must be made for the degree of prematurity.

*Physical development*: Weight, length and other measurements all reach normal limits between two and five years, the female catching up before the male, and the baby with the larger birth weight before the baby with the smaller birth weight.

Prematurity *per se* does not alter the normal course of *mental development*, but allowances must be made for the degree of prematurity. Reports have been made of speech defects, temper-tantrums, diminished self-reliance, enuresis, thumb sucking and other habits, but so far there has been no well-controlled investigation into the behaviour development of premature babies. Research is necessary in this field, and if a higher incidence of behaviour problems is found in the premature infant then investigation is required to discover whether this is due to prematurity or to over-protection of premature babies.

Alm of Stockholm has followed up 1,000 males born between 1902 and 1921. He reports that, unless maimed at birth, 70–80% of premature babies make slightly better grades at school than average, that fewer premature babies are criminals, and that premature babies can command an average income.

According to investigations made in Birmingham (7,000 premature babies and 3,000 babies weighing over 5½ lb. followed to the age of 1 year), of every 100 prematures that are born, 17 die before reaching the age of 1 year, and only 2 of the 83 remaining babies show any physical or mental defect. In comparison, of every 100 babies over 5½ lb. at birth, 2 die before the age of 1 year, and of the remaining 98 1 is defective. These figures include all infants born with fœtal abnormalities as well as those who subsequently suffer complications.

**Dr. J. W. B. Douglas** (Director, National Survey of the Health and Development of Children): For the last seven years a Joint Committee[1] of the Institute of Child Health, the Society of Medical Officers of Health, and the Population Investigation Committee has been following up a national sample of premature children each of whom has been matched with a carefully chosen control. The premature children were all those born in 424 maternity and child welfare authorities in England, Wales and Scotland during the first week of March 1946. They have been matched with mature children born during the same week who were of the same sex and place in the family, who came from the same type of home and lived in the area of the same maternity and child welfare authority. This note describes some aspects of their health and growth during the first four years of their lives; in this period, apart from losses from death and emigration, only eight pairs of children have dropped out of the inquiry.

The health of these children has been described in a recent article (Douglas and Mogford, 1953). During the first two years premature children were three times as likely to be admitted to hospital as their controls; this excess of hospital care was largely explained by a higher incidence of infections, particularly of the lower respiratory tract. At later ages they were no more likely to be admitted to hospital. Even during the first two years the calls made on the hospital services by premature children were not large; they contributed 11% of all admissions during this period, as compared with an expected 4%.

Fig. 1 shows the weights and heights of premature children and their controls at different ages.

It will be seen that the premature children were as much behind their controls in weight at 4 years as they were at birth, and as much behind them in height at 4 years as they were at 2. There were, of course, considerable differences in the rates of growth of individual premature children and approximately 40% of them had eliminated their initial physical handicaps by 4 years. It will be seen in Table I that the premature children who caught up in this way have mothers that were drawn from the same weight and height populations as the mothers of the controls, whereas those who did not catch up had mothers that were significantly lighter and smaller.

TABLE I.—WEIGHT AND HEIGHT DIFFERENCES BETWEEN THE MOTHERS OF CONTROLS AND THE MOTHERS OF PREMATURE CHILDREN

| | Premature children having caught up | Premature children still handicapped |
|---|---|---|
| Mothers' weight difference .. .. .. .. .. | 1·9 ± 2·2 lb. | 12·6 ± 2·6 lb. |
| Mothers' height difference .. .. .. .. .. | 0·12 ± 0·34 in. | 1·82 ± 0·31 in. |

In general it appears that the measurements of the parents give the best indication of the subsequent growth of a premature baby.

While premature children contribute more than their share of the stunted and underweight children

[1]The chairman of the Committee is Professor James Young, the vice-chairman Professor A. A. Moncrieff and the secretary Professor D. V. Glass. The Nuffield Foundation has financed this inquiry during the pre-school years, and a grant for continuing it in the primary school period has been made by the Board of the Hospital for Sick Children, Great Ormond Street, through the Institute of Child Health.

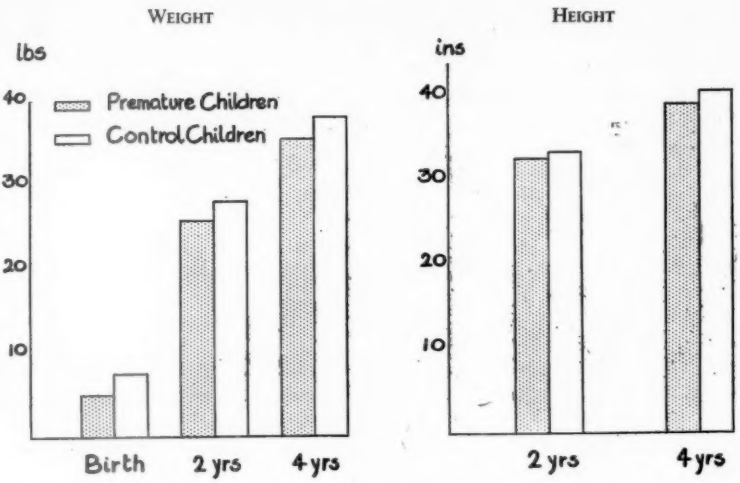


FIG. 1.—Comparison of the weights and heights of premature children and their controls.

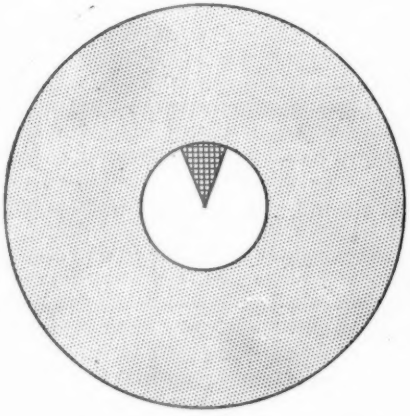

FIG. 2.—Proportion of all stunted or underweight children that were prematurely born.

Area of larger circle represents all children in main sample.

Area of smaller circle represents proportion of all children who were stunted or underweight.

Segment of smaller circle shows proportion of stunted or underweight children who were premature.

in the whole population, only a relatively small reduction in the numbers of these children would be brought about if all premature births were prevented. This is shown diagrammatically in Fig. 2 where a stunted or underweight child has been arbitrarily defined as one who at both 2 and 4 years was more than one standard deviation below the mean weight or height for all children of that age.

In short this study gives little support to those who see in prematurity a major source of ill-health and retarded growth.

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**Dr. H. M. Mackay:** It is well recognized that a premature infant may have a subnormal body temperature because he has an infection, or may develop such an infection because chilling has lowered his resistance, hence the importance of treating all such infants with antibiotics without waiting for clinical signs of infection. To those like Dr. Trevor Mann, who consider that a rectal temperature of 97° F. is normal for a premature infant, I can only suggest that they compare the vigour of babies whose temperature fluctuates between 96 and 97° F. and those whose temperature is between 98 and 99° F. I am in no doubt that the premature infant is not at his best with a rectal temperature of 97° F.

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JOINT MEETING No. 5

# Section of Neurology with Section of Comparative Medicine

Chairman—Professor F. J. NATTRASS, M.D.
(Vice-President of the Section of Neurology)

[*April* 9, 1953]

## DISCUSSION ON SOME NEUROLOGICAL DISEASES OF MAN AND ANIMALS

**Dr. E. Weston Hurst** (Imperial Chemical Industries Limited, Biological Laboratories, Manchester):

### *The Demyelinating Diseases of Man and Animals*

The demyelinating diseases are those affecting predominantly, though not necessarily exclusively, the white matter of the brain and spinal cord, and which are not obviously secondary to disease in, or lesions of, the nerve cells or their processes.

The current stains for myelin are sadly lacking in their ability to reveal the finer differences in a morbid anatomical picture. There have been two regrettable consequences of over-dependence on the myelin stain, the first a tendency to group together wholly dissimilar pathological conditions because demyelination is a feature of each, the second and even more frequent tendency, whenever demyelination has been produced experimentally, to claim that the experimental procedure involved points to the cause of one or other human disease, and most commonly of disseminated sclerosis. Thus, under certain circumstances, vascular blockage may lead to demyelination, and thrombosis has been held to be a causative factor in disseminated sclerosis; in the opinion of most, however, it is not the cause of that disease. Again, when some years ago I produced demyelination of the centrum semi-ovale by poisoning monkeys with potassium cyanide, the claim was attributed to me to have reproduced Schilder's encephalitis—a claim which I did not make.

In toxoplasmosis undeniable evidence exists that the condition in man is the exact counterpart of that occurring spontaneously, or provoked experimentally, in animals, and *vice versa*. Not so with the demyelinating diseases. Tables I and II indicate the heterogeneity of the pathological states grouped together as the so-called demyelinating diseases of man and animals. Of course, we must consider the possibility of some deep underlying unity of these superficially different conditions, a unity possibly overlaid and masked by different types of reaction to a single noxa by the tissues of different animal species. I think that we can dispose of this theoretical possibility forthwith. Demyelination can be produced experimentally in animals by a number of different procedures (Table III), and the results of applying any particular technique are essentially the same, or at least reasonably similar, whatever the species of animal used for experiment. The greatest species variation probably occurs in allergic encephalitis—it is universal knowledge that the manifestations of allergy differ somewhat in the various animal species. The lesions of allergic encephalitis as we move from species to species are not, however, so dissimilar as to suggest that we are dealing with wholly different pathological conditions. These observations show that, basically, the nervous tissues of widely different animal species respond in the same general way to a given pathological stimulus. Returning, then, to the very heterogeneous group of demyelinating diseases of man and animals, we are almost compelled to postulate several different ætiological factors, and to admit that we are dealing with a number of quite dissimilar diseases.

A second point emerging from the tables concerns the many gaps, question marks and statements of the unknown there displayed. With the probable exception of the post-vaccinal type of encephalitis, we do not know precisely how any of the human demyelinating diseases is brought about, and it is more than doubtful whether any of the means by which demyelination may be produced in animals really offers a lead to the ætiology of, say, disseminated sclerosis or Schilder's encephalitis in man.

We seldom learn much about the causation of a human disease until we are able to reproduce and study it in the laboratory. For that reason, and because repeated attempts to transmit various human demyelinating diseases to animals had failed, some years ago I thought that it might be profitable to neglect for the time being attempts to transmit specific diseases, and to find out in what ways demyelination can be produced in the experimental animal. Some of the results may be summarized briefly.

TABLE I.—SOME DEMYELINATING DISEASES OF MAN

| Disease | Probable or possible equivalent in animals | Cause |
|---|---|---|
| Disseminated sclerosis .. .. | — | Unknown |
| Schilder's encephalitis and variants both familial and otherwise | — | Unknown |
| Metachromatic leuco-encephalopathy | — | Unknown |
| Neuromyelitis optica .. .. .. | — | Unknown |
| Acute disseminated encephalomyelitis | — | Unknown |
| Post-vaccinal and similar forms of encephalitis | Paralytic accidents in dogs undergoing antirabic treatment | Probably allergy |
| Acute hæmorrhagic leuco-encephalitis | ? Acute epizootic leuco-encephalitis of horses | Probably allergy |
| Subacute combined degeneration .. | ? So-called cage-paralysis of apes, monkeys and lemurs | Nutritional deficiency |
| Inclusion encephalitis .. .. .. | — | Probable virus |

Demyelination also described in a variety of toxic and nutritional disorders—ergotism, tetanus, liver disease, eclampsia, alcoholism (Marchiafava's disease), &c., as well as in some viral and bacterial encephalitides and with severe cerebral œdema.

TABLE II.—SOME SPONTANEOUS DEMYELINATING DISEASES OF ANIMALS

| Disease | Probable or possible equivalent in man | Cause |
|---|---|---|
| Distemper and possibly other virus diseases of dogs. "Acute multiple sclerosis" of dogs | Areas of demyelination in equine encephalomyelitis, Australian X disease, &c. | Attack of a virus on the white matter in former group. Status of "acute multiple sclerosis" uncertain |
| So-called cage-paralysis of apes, monkeys and lemurs | Subacute combined degeneration | ? Nutritional deficiency |
| Swayback of sheep .. .. .. | — | Copper deficiency |
| Acute epizootic leuco-encephalitis of horses | ? Acute hæmorrhagic leuco-encephalitis | ? Allergy |
| Encephalitis of moose .. .. | — | ? Nutritional, ? toxic |

TABLE III.—MEANS OF PRODUCING DEMYELINATION EXPERIMENTALLY

| Experimental procedure | Probable or possible equivalent in man |
|---|---|
| Vascular occlusion, especially of capillaries or of venules | Binswanger's disease; some cases of fat-embolism |
| Poisoning with potassium cyanide or sodium azide; simulated high altitudes | Demyelination after carbon monoxide poisoning |
| Repeated injection of brain tissue .. .. | Paralytic accidents of antirabic treatment; post-vaccinal and similar forms of encephalitis |
| Production of the Arthus reaction intra-cerebrally | ? Acute hæmorrhagic leuco-encephalitis |
| Experimental canine distemper .. .. .. | Areas of demyelination in equine encephalomyelitis, Australian X disease, &c. |
| Infection of mice with the JHM virus .. .. | As preceding |

Reports, mostly in the older literature, describe demyelination after poisoning with guanidine, staphylococcal toxin, dysenteric toxin, saponin, vinilamine and products of *Aspergillus fumigatus*.

Potassium cyanide causes anoxia of the tissues by paralysing the intracellular respiratory ferments. After repeated daily treatment of monkeys with a dose somewhat short of the lethal, there comes a time when the animal suddenly develops severe nervous symptoms after an injection previously tolerated on 12–20 occasions. Such animals show massive necrosis of the centrum semi-ovale, with preservation of the U-fibres as occurs in Schilder's disease in man; areas of necrosis also occur in the basal nuclei. If a single still larger dose be given, from the effects of which the monkey dies in twenty-four to forty-eight hours, this picture is seen but seldom; instead there is laminar necrosis of the cerebral cortex. With repeated smaller doses over many months a true demyelinating lesion develops in the centrum semi-ovale. Thus the sequence of lesions with diminishing dosage is:

(1) Very large single dose—cortical necrosis—only occasionally necrosis of the centrum semi-ovale.
(2) Repeated large doses—necrosis of the centrum semi-ovale and basal nuclei—cortex intact.
(3) Repeated smaller doses over a longer period—demyelination of the centrum semi-ovale.

With sodium azide, another substance inhibiting cellular oxydases, necrosis or demyelination can also be produced at will, according to the dosage. Here, however, lesions in the centrum semi-ovale are infrequent; instead the optic nerves and tracts suffer most severely.

Morrison in the United States produced lesions like those in cyanide poisoning by simulated high altitudes, showing that the effect of cyanide or azide is in no way specific but merely a result of anoxia of the tissues.

In other experiments small vessels were blocked by globules of "mayonnaise". Blockage of single capillaries usually leads to no change, of a small group of adjacent capillaries to demyelination, of a dense mass of capillaries or of a larger vessel to full necrosis of the tissue—the same sequence of changes according to the intensity of the pathological process. Some years previously, of course, Putnam had produced demyelination by blocking venules and other small vessels.

In some virus diseases, also, areas of necrosis in the white matter may alternate with foci of demyelination according to the severity of the lesions in a particular spot; a good example is dog distemper, in which disease demyelination is more conspicuous than in most virus diseases.

At this point we may perhaps enquire whether this sequence of necrosis—demyelination—no change, according to the local intensity of the pathological condition, is purely an experimental quirk or whether it has any counterpart in human pathology. A case I saw just before returning from Australia, and which unfortunately has never been published, suggests that analogous behaviour may occur in man and may be seen if circumstances favour the observer. A young and apparently healthy woman fell off her bicycle in the street, had difficulty in rising, and was admitted to hospital with a lumbar myelitis which in the course of ten days or so gradually ascended to the mid-dorsal region. At this point she died suddenly of a pulmonary embolism. The lumbar cord was diffluent and consisted microscopically of little else but meninges, proliferating vessels and scavenger cells. The mid-dorsal cord was quite different—it showed a recent acute necrosis of the white matter, complete save for the meninges and the vessel walls, with no reaction save a very scanty infiltrate of mostly karyorrhectic polymorphs—a picture essentially similar to that produced by potassium cyanide in the centrum semi-ovale of monkeys. A careful routine examination of other levels of the nervous system revealed nothing but a large demyelinated plaque, obviously of some standing, in the cerebellar white matter—in life there had been no symptoms to suggest its presence. Now, unless we postulate the co-existence in the nervous system of this case of two separate and unrelated pathological conditions, with the demyelinated plaque wholly unaccounted for, we must look for a single causal agent acting in different intensity, in different places, at different times.

It seems then that demyelination is the characteristic response of the white matter to pathological stimuli insufficiently severe to cause full necrosis of the tissue, and that many pathological stimuli are capable of producing it.

No consideration of the demyelinating diseases would be complete without brief mention of the now well-known allergic encephalitis. Such encephalitis has been induced in monkeys, dogs, sheep, rabbits, guinea-pigs, rats and mice by injecting heterologous or homologous brain emulsions, and, most significant, by using even an excised portion of the animal's own brain. In most if not in all animals, demyelination of some degree or other forms part of the morbid picture. Current belief links the experimental condition with the post-vaccinal type of encephalitis in man. Ferraro, however, has gone further, and has sought to explain the pathology of all human demyelinating disease as an allergic response on the part of the nervous system. Looking over the whole range of human and animal diseases in which demyelination is a conspicuous feature, and comparing the histological lesions of the different diseases, it seems almost impossible that a single explanation can cover the lot. Even if Ferraro's opinion be accepted, however, it would not necessarily dispose of the ætiology of, say, disseminated sclerosis. We should need seriously to consider whether allergy to the extraneous or endogenous antigen were the primary condition initiating the nervous lesions, or whether in the course of a destructive disease due to unknown causes the patient became sensitized to products of breakdown of his own nervous tissues.

Everyone, of course, must reach his own conclusions. Mine can be stated in a very few words:

(1) The demyelinating diseases of man and animals are heterogeneous.

(2) We have no precise knowledge of the cause of most of them.

(3) We must be suitably critical in drawing conclusions from experiments, past and future, in which demyelination is produced by one means or other, and in attempting to relate the experimental results to the unsolved problems of human neurology.

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**Dr. David Trevan** (Wellcome Laboratories, Beckenham, Kent):

*Early Lesions in "Nervous Distemper" of Dogs*

The viruses of the dog-distemper group are not the only ones known to be capable of causing demyelination, but I think that they are the only potentially demyelinating viruses which can in addition, and in the same animal, affect such a variety of tissues, mostly epithelia, outside the nervous system. This affinity for epithelia is paralleled by the preference of the virus for peripheral (submeningeal, subependymal) sites in the central nervous system; demyelination in early cases is usually in such sites, the almost sole exception to this being the demyelinating lesions found in the white matter of cerebellar folia. Lesions in later cases may be superficial or deep, and are associated with perivascular inflammation which is absent or minimal in early lesions, where inflammation is only glial. In spite of the larger extent of lesions in later cases, it has often not been possible to obtain from the brain of such cases an agent infective for ferrets or for dogs; whereas from brains showing lesions of the early type a virus of the distemper group can usually be recovered. It is not yet certain that we shall have to assume a cause other than a distemper virus for some cases of the second type; some strains of virus have a very long incubation period in the ferret, so that we may have missed them by not waiting long enough for the ferrets to show symptoms; and it is possible that the demyelinating process may continue, as an "allergic" reaction, after the virus that started it has died out. I must not press this hypothesis, which has not been tested and which it seems very difficult to test: I shall at present describe only the peripheral, glial lesions, which appear to be directly due to invasion by virus, as seen in 3 early cases of "nervous distemper".

The first case is that of a 3-month-old labrador, which was destroyed about a day after the onset of continuous convulsions; it had been ill for four or five days previously, with discharge from the nose and eyes. Other pups in the litter were similarly affected; the dam had been immunized against distemper eighteen months before, and had suffered, three weeks before the pups became ill, a mild febrile tonsillitis, from which she recovered uneventfully. The only conspicuous brain lesion in this pup was found in the ependyma on the ventricular surface of the cerebellum. The ependyma cells were distorted, heaped up, and exfoliating; they contained many large nuclear and cytoplasmic inclusions. The underlying white matter was œdematous, and swollen macroglia near the surface contained similar inclusions, but there was no glial proliferation, and no demyelination. The epithelium of the choroid plexus of the fourth ventricle contained many large cytoplasmic and nuclear inclusions.

The second case is that of a 3-year-old dachshund that had had convulsions, and no other symptoms, for eighteen days before it was destroyed. There was a patch of demyelination in what is a common site in our cases, around the base of a deep sulcus in the lateral edge of the cerebellar hemisphere; in this situation in the dog there is no cortex covering the white matter, so that the latter is covered only by meninges. The demyelination was most intense near the surface, and affected both cerebellar hemispheres symmetrically. There was no meningitis, and no vascular cuffing in the affected area; glia had proliferated and swollen, and contained nuclear and cytoplasmic inclusions; the cytoplasmic ones were fewer and smaller than those seen in the first case. Damage to axis cylinders in the area was slight or absent, although they were pushed apart by the œdema and glial proliferation. The only other nervous lesion of note consisted of areas of cerebral cortex showing gliosis and inclusions in the cytoplasm and nuclei of large nerve cells, as well as in neighbouring glia; these lesions might account for the convulsions. The cerebellar lesion was small enough to be symptomless.

The third case is that of an adult spaniel from a kennels where a chronic insidious nervous disease, characterized by repeated fits and inco-ordination of gait, was enzootic. The duration of illness in this case was not known, but a week before death there was a major fit from which the dog never fully recovered consciousness. There were no obvious lesions to account for this, in the cerebral cortex; but in the cerebellum was found a large submeningeal area of demyelination in which were proliferated glia and compound granular cells. Inclusions were far fewer than in the second case, although the damage was more severe and extensive. They were mainly nuclear, in astrocytes, distinguishable from the nucleolus by being more acidophil. Cytoplasmic inclusions were hard to find, and minute, in swollen protoplasmic glia. On the other hand, nuclear inclusions could be found in astrocytes in white matter far from the area of demyelination; and this is a usual finding in such cases.

Thus, in the later lesions of "nervous distemper", only nuclear inclusions remain as evidence of virus activity; the fact that they are associated with many large cytoplasmic inclusions in the earlier lesions suggests that they are indeed of "virus" origin. The disappearance of cytoplasmic inclusions in later lesions parallels the difficulty one has in isolating virus from the brains of late cases showing large demyelinating lesions, and suggests that there is in such cases less virus, or a less active form of virus, although demyelination is apparently proceeding.

**Mr. H. B. Parry** (Animal Health Trust): Most disorders of the nervous system of dogs are commonly attributed to distemper virus infection, but when considering the role of this infection in the production of demyelinating and other pathological lesions under natural conditions it is prudent to examine more closely the syndromes encountered and the viruses responsible.

Slides were shown to illustrate three types of syndrome:

I. Canine hepatitis virus infection: diffuse encephalopathy with motor seizures during the febrile period with recovery within seven days without neurological or other sequelæ for fifteen months thereafter.

II. Canine distemper-complex virus infection: localized damage to the brain-stem in the immediate post-febrile period producing a trochlear palsy lasting for forty-eight hours only and a vestibular defect which persisted.

III. Canine distemper-complex virus infection: chronic delayed secondary encephalopathy occurring twelve to eighteen months after the acute primary encephalopathy with the gradual onset of blindness, loss of the electroretinogram and personality changes. Cystic encephalomalacia of the grey matter was found at autopsy.

These cases occurred in isolation kennels under experimental conditions and the nature of the infection was established in each case. They illustrate the variety of clinical syndromes which occur and suggest the need for their definition before attempting to classify these disorders on histopathological criteria alone; indeed in some epidemics of distemper-complex infection cases of acute fatal encephalopathy occur in which morphological lesions cannot be found.

**Dr. A. M. G. Campbell:**

*Toxoplasmosis*

Dr. Macdonald Critchley emphasized at the joint meeting of the Sections of Neurology, Orthopædics and Pædiatrics on February 5, 1953, the importance of intra-uterine infections as a possible cause of neurological conditions hitherto unexplained. It was not until 1939 that Wolf, Cowan and Paige showed that the protozoon toxoplasma was responsible for infection of the fœtus *in utero*, the mother often being perfectly normal. Various abnormalities in children such as encephalomyelitis, choroidoretinitis, mental deficiency, defective vision, intracerebral calcifications and hydrocephalus were also traced to toxoplasma infection. They also showed that this human infection was identical with the infection found in many animals such as dogs, cats, rats and birds and managed to transmit infection from human cases to mice, producing encephalitis.

Infection in animals has been known since 1909 and human infection had been found in the eye in 1923.

The organism is a crescentic protozoon, which can invade any tissue, but has a predilection for the tissues of the nervous system and the eye. The organism multiplies by simple binary fission and is intracellular and forms groups or pseudo-cysts with clusters of organisms, which may degenerate to form large granulomata. It cannot live outside the cell.

Organisms have been found in almost every tissue of the body and cases of the disease have been reported from almost every country in the world. In Great Britain the disease was not recognized for some time and it was not until 1948 that the first infantile case was reported by Jacoby and Sagorin.

It is now clear that the disease falls into three main groups: (1) Congenital. (2) Acquired disease in adults and children. (3) Latent disease, with pathological findings, but no clinical findings.

The extreme rarity of active toxoplasmosis in adults is in contrast to the apparently widespread occurrence of the parasite in the animal kingdom.

Recently, from the work of Sabin (1941) in the United States, it has become clear that an increasing number of the population acquire a subclinical infection of the parasite with increasing age and that positive antibody and skin sensitivity tests are more numerous with increasing age and are found in from 40% to 60% of the adult population. In the majority of these people their symptoms are inconspicuous or absent and they are never diagnosed.

Some writers consider the disease flares into activity during pregnancy and may, as in a case seen by the author, cause a maternal rash in pregnancy. The susceptible fœtus may suffer severe damage, although the mother remains relatively well. It must be added that Sabin believes that the mother acquires the infection during her pregnancy and not that it was present before and flared into activity due to pregnancy. The matter is quite undecided at the moment, but it does appear to the author to be more likely that the disease is present and becomes active during pregnancy.

We are, at the moment, unable to say how the disease is transferred from animals to man, but many of the cases which have been recorded have had contact with a sick animal.

Recently Cowan and Wolf (1951) in the United States have managed to produce congenital toxoplasmosis in mice by infecting the mother through the vagina. It is possible that this may have some importance in the human disease, but one of the most important facts which remains to be discovered about this condition is just how human beings are infected.

The chief signs of the infantile form of the disease are:

(1) Meningo-encephalitis.

(2) Ocular signs, such as optic atrophy and choroidoretinitis.

(3) Intracerebral calcification.

(4) Hydrocephalus and general enlargement of the ventricular system. This may be accompanied by severe mental retardation.

Many of the children will die early in the first few weeks of life or may even be born dead. In

some of these cases any degree of active infection will burn itself out and although pathological testing usually shows antibody response, some show a negative serology. It is probable that even when the disease is clinically quiescent, the pseudo-cysts in the brain contain virulent material and organisms capable of activity and the material from these cysts has been capable of infecting animals despite the apparent quiescence of the disease.

Considerable help in diagnosis may be obtained from a study of the eyes, which may show choroidoretinitis especially near the macula, microphthalmus, optic atrophy or alteration in the pupils, and in the congenital cases, considerable help is obtained from the presence of cerebral calcifications, which usually take the form of linear calcifications, in the region of the ventricles and basal ganglia. Calcification is rarely demonstrated in adults, but can begin in the fœtus *in utero*. The cerebrospinal fluid shows an increased protein and increased cell count and may be under raised pressure.

The number of infantile cases recorded in this country is steadily growing and it has become obvious that a number of minor cases which are primarily congenital in origin become noticed at a much later date because of the development of some new complication, such as epilepsy or mental retardation; some of the cases recorded by Hart *et al.* (1951), although of congenital type, were not diagnosed until the patients had reached their teens.

Table I shows a family which became recognized because one of the children has macular choroidoretinitis, optic atrophy and hydrocephalus and is, at the moment, in a Blind School. This child is the only child severely infected, although it is possible that one child died of the disease at birth; all that is known is that the child died of jaundice. The third child is perfectly normal and the fourth child, by a different husband, is again perfectly normal. It is interesting that this child showed antibodies, acquired from the mother, for about six weeks and then became negative. It is probable that antibodies and the infecting agent pass to the fœtus together in varying quantity and one of the reasons why the eye and the central nervous system are so severely affected is considered to be that the antibodies reach these with great difficulty.

FIG. 1.—Rash seen in adult toxoplasmosis.

Yet another case developed a severe macular rash (*see* Fig. 1) during her pregnancy and her child was a mental defective and hydrocephalic. Both mother and child, and subsequent children, have shown marked antibody responses. The development of rashes during pregnancy must always suggest some toxoplasmosis activity.

In America, latent cases have been demonstrated in drowned persons in which the disease has not been suspected, indicating quiescence for long periods and supporting the theory of a flare-up of the disease during pregnancy. Also, if the mother had acquired the disease during pregnancy, it is surprising that she does not show severe symptoms, but rather more often shows no symptoms at all, or only a rash.

Johnson (1946) has recorded a case of a mother who, during three successive pregnancies, showed a flare-up of her choroidoretinitis, which was due to toxoplasmosis, the ocular condition remaining quiescent between the pregnancies.

## THE DISEASE IN ADULTS

Sabin described an acquired form of the disease in older children and stressed the slightly different features of this illness and as early as 1914 Castellani had found an organism resembling toxoplasmosis in a Sinhalese boy of 14 years, dying of an unknown fever and enlargement of the spleen. It was not until 1941 that Pinkerton and Henderson described an acute illness in adults, resembling typhus fever, in which there was a macular rash, temperature and pulmonary signs and in whom toxoplasmosis was found at post-mortem. In one of their patients, the disease was successfully transmitted to guinea-pigs.

Several cases have been described since this date, one by Syverton and Slavin (1946), with fever, diarrhœa, joint pains and again a macular rash with a marked eosinophilia, from 25 to 45%. In this case, the man had an unexplained rash twenty-five years previously, which may have been a manifestation of the infection.

Other cases of febrile illness have recently been described, which have been found to be adult toxoplasmosis. Several cases have been recorded in Germany and America and particularly important in the American cases is one recently recorded by Kass *et al.* (1952) in which the disease attacked a 60-year-old woman, who was admitted to hospital with a generalized macular rash, aching pains and fever. This is an interesting case because toxoplasmosis was considered as a diagnosis, but the skin reactions were negative on the twelfth day of the illness, and this diagnosis was discarded.

A biopsy was taken from the left calf muscle on the thirty-fifth day and toxoplasma organisms were found. It was then decided to repeat the tests, which had now become positive. The antibody response had not taken place for some three or four weeks after the illness had commenced. This patient eventually died on the sixty-second day of the illness and toxoplasmas were found throughout the body, including the myocardium and brain. This was an acute fatal case, running an unrelenting course in an elderly woman, who showed no response to any form of treatment. There was, at one stage of the illness, a lymphocytic meningitis and on the twenty-first day the patient showed evidence of cerebral damage. During the illness there was a marked eosinophilia and at one time the case was thought to be periarteritis nodosa, which led to the biopsy from the calf.

The importance of the case is that it was undoubtedly an acquired infection and acquired in such an elderly individual, who as far as is known, had had no contact with any animal which might have been considered the reservoir of the infection. Also diagnosis was made by biopsy for the first time.

In the United States, as Kass *et al.* (1952) point out, in at least 4 cases the serological data indicated that the disease was acquired and not congenital and in 3 of these cases, toxoplasmosis occurred in laboratory workers, 1 of which had a fatal outcome. It seems wise, therefore, not to permit workers to deal with toxoplasmosis if they do not have antibodies to the organism before working with such material.

Secondly, toxoplasmosis should not be discarded as a diagnostic possibility unless sera is examined well after the fourteenth day of an acute illness.

The disease in adults takes the form of a generalized systemic infection of a large number of tissues, but, in particular, it appears to affect the brain, lungs, liver and spleen, and to a much lesser degree the eye, than do the congenital cases. The diagnosis must be considered in any case of pyrexia of unknown origin, particularly when a chronic macular rash is present. The rash is a very important diagnostic feature.

TABLE I

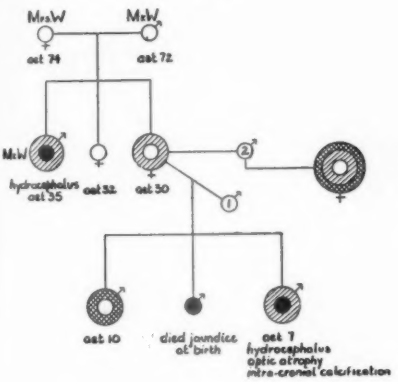
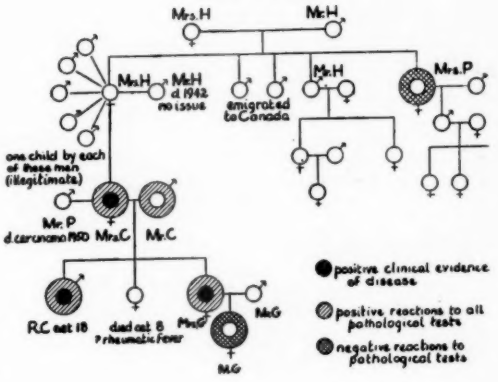



TABLE II




We have recently studied a family (Table II) which, although of congenital origin, indicates a considerable link between the symptoms shown by the congenital cases and those described as acquired (Campbell and Clifton, 1950). This family consists of a mother, Mrs. C., and two children, who have all suffered from a periodic maculo-papular rash, periodic joint pains, inflammation of the conjunctivæ and persistent headaches. On examination, all have been found to have meningo-encephalitis, nerve deafness and either swollen optic discs or optic atrophy.

The picture in these cases resembles congenital syphilis, but all the serological tests for syphilis were negative and all tests for toxoplasmosis, including a toxoplasmin test, were positive. There was a marked degree of eosinophilia in the blood, and the cells in the cerebrospinal fluid also showed an eosinophilia of 10%.

The exact origin of the infection was unknown and treatment was entirely unsatisfactory. This family is remarkable in that the infection appeared to have persisted for many years, without killing the patients, but was sufficient to produce quite severe physical symptoms.

Recently, the mother of the family has died and at post-mortem was found to have an abscess in the spleen.

Histological studies by Dr. Valentine have failed to prove any evidence of toxoplasmosis in the body. The brain showed a chronic meningo-encephalitis, consistent with the clinical picture and marked amyloid changes were present in the liver, kidneys and spleen, probably consistent with the

chronic infection having been present for such a long period. Thus, histologically we have failed to prove that this family has toxoplasmosis. On the other hand, it is very difficult to think of an alternative diagnosis and in such a chronic condition it would, I think, be unlikely to find the organism. Congenital syphilis being excluded, we feel it is the most likely diagnosis despite the negative histological findings.

During life, this patient had an enlarged spleen and also evidence of a fairly acute meningo-encephalitis.

The grandchild M. G., (now aged 4 years) of the most severely affected case was found to have a rash of the same type as the other cases, but the antibody responses were negative.

The symptoms shown by this family were very similar to the acquired case of the disease described by Kass *et al.* (1952) and also a case described by Brennan *et al.* (1949), in which there was choroidoretinitis, cutaneous eruptions and persistent and fluctuating headaches.

It appears, therefore, that the diagnosis of this disease may be recognized on clinical grounds and can be confirmed by pathological tests, of which the complement-fixation test or the cytoplasm modifying test and the toxoplasmin skin test are all valuable. It is sometimes extremely difficult to obtain evidence during life of the organism and we failed to find organisms in the brain tissue or in the cerebrospinal fluid in our cases.

Valentine (1953) is the only person in this country to have found the organism in any case, either during life or after death. In an adult case which resembles toxoplasmosis it appears justifiable to consider a muscle biopsy as a diagnostic measure.

At the moment, we have no drug that will attack this disease, although sulphonamides have been found to protect animals from infection. Obviously they do not affect the pseudocysts and it is unlikely that any chemotherapeutic substances could penetrate this pseudocyst membrane.

Luckily even if a large number of people are infected by this condition, it only endangers the lives of a very small number, but it is obviously important to consider the possibility of this condition in an unexplained illness with the symptoms previously described, particularly if the patient has had any contact with animals. It is probable that the majority of human cases originate from infection acquired from dogs, rabbits, rats and birds, as the condition is widespread in the animal kingdom.

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**Mr. T. W. F. Pay** (Department of Pathology, Royal Veterinary College): Spontaneous cases of toxoplasmosis have now been reported in some 24 different mammalian species, including the rabbit, hare, guinea-pig, mouse, rat, vole, squirrel, mole, monkey, dog, cat, sheep and pig. Toxoplasmosis has also been recorded in about 45 different species of bird, but Manwell *et al.* (1945) have shown that the so-called avian toxoplasmosis is not capable of infecting mammals and does not protect birds from infection with the mammalian strain. True mammalian toxoplasma infections, however, do occur in pigeons, domestic fowls and other birds. In the majority of instances, when the organism was first discovered in a new host it was described as a new species. However, it is now generally accepted that all strains of toxoplasma, regardless of their source, are biologically identical and are of the same species *T. gondii*.

It is not possible in the short time available to describe in any detail the characteristics of toxoplasma or to survey the whole field relating to toxoplasmosis in animals. Therefore, I shall restrict my remarks mainly to toxoplasmosis in the dog, as there is probably more information available concerning this infection in the dog than in other domestic animals, and the public health aspect is obviously of major importance.

The first case of toxoplasmosis in the dog was reported by Mello in Italy during the year 1910. Since that date cases of this infection in dogs have been reported in sixteen different countries all

over the world, and it is now clear that what was thought to be a disease of the tropics is in effect one of universal distribution. Table I shows the countries in which toxoplasmosis in the dog has

TABLE I.—TOXOPLASMOSIS IN THE DOG

| Country | Dates reported | Country | Dates reported |
|---|---|---|---|
| Italy .. .. | 1910 | India .. .. | 1941 |
| Germany .. | 1911, 1950, 1951 | Japan .. .. | 1939 |
| France.. .. | 1921 | Morocco .. | 1949 |
| Denmark .. | 1947, 1948, 1951 | Tunis .. .. | 1917 |
| Great Britain .. | 1949 | Brazil .. .. | 1911, 1913 |
| Switzerland .. | 1950, 1951 | U.S.A... .. | 1942 |
| Turkey .. | 1950 | Canal Zone .. | 1950 |
| Iraq .. .. | 1939 | Australia .. | 1950 |

been reported and the dates of each report. It can be seen that the more recent recognition of toxoplasma infection in man has probably accentuated the recognition of it in the dog.

*Symptoms.*—In discussing the clinical picture of toxoplasmosis in the dog it will be useful to compare the various manifestations observed with those seen in man. Thus, the majority of the cases reported in the literature ran a course similar in many respects to the acute exanthematous fever first described in the adult human by Pinkerton and Henderson (1941). The commonest signs exhibited were those resulting from involvement of the lungs and gastro-intestinal tract, namely dyspnœa and diarrhœa or dysentery. These were usually accompanied by fever, loss of appetite and rapid emaciation. Although the liver is commonly affected, often extensively, there is only one report in the literature of a case showing clinical jaundice. Many authors have stressed the resemblance of the clinical picture to that of distemper. Møller (1951) described a case in Denmark in which he was also able to demonstrate typical distemper virus inclusion bodies and he postulated that distemper may precipitate the exacerbation of a chronic infection or increase the susceptibility to toxoplasmosis. I feel, however, that if toxoplasmosis were a common accompaniment to distemper many more cases would have been found by workers studying this virus disease in the dog.

It is interesting to note that despite the well-known "neurotropic" character of toxoplasma, not one out of the 23 cases described by 15 different authors previous to Fankhauser's recorded cases in 1950 showed clinical evidence of involvement of the C.N.S., although in 2 cases the organism was found in the brain at autopsy.

Fankhauser (1952) has described 20 cases found by him in Switzerland. He divides the clinical picture into two distinct syndromes. One associated with gastro-enteritis, liver damage, splenomegaly, pneumonia, pustulous exanthema, and other less marked and constant symptoms; and another associated with involvement of the C.N.S., manifested by psychic disorder, paraplegia, disturbances of skin sensitivity and tendon reflexes, myoclonia, epileptiform attacks and increased protein and cell content in the C.S.F. In contrast to toxoplasmosis in the human, no cases of congenital infection with the associated clinical manifestations of hydrocephalus, microcephaly, chorioretinitis and cerebral calcification have been described in the dog, although congenital infections have been produced by the experimental inoculation of pregnant bitches (Chamberlain *et al.*, 1952).

*Pathology.*—A form of C.N.S. involvement seen in the dog unreported in the human is the production of single or multiple discrete focal lesions. Fankhauser (1952) found 4 such cases in his series of 20 and Cohrs (1951) described a similar case. In 1949 two of my colleagues, Mr. W. Plowright and Dr. F. Bell, examined a greyhound which had been presented with the history that it had raced normally on Saturday, November 5, and on Monday, November 7, it had developed a marked ataxia and evidence of vestibular involvement, manifested by rolling to the right. The dog was kept under observation but was finally destroyed on November 16. Autopsy revealed a focal lesion approximately 3 to 4 mm. in diameter in the superior medulla involving the root of the VIII nerve and the vestibular nucleus on the right side. Histological examination of the lesion showed it to consist of an area of necrosis infiltrated with large compound granular corpuscles. In and immediately around the lesion could be found toxoplasma pseudocysts, but no free forms. No other lesions were found elsewhere in the C.N.S. or in the visceral organs and no organisms could be demonstrated in any other site. The rarity of focal hæmorrhage of the brain of the dog due to vascular disease would warrant the suspicion of toxoplasmosis being the cause of any case showing evidence of focal brain damage of sudden onset.

Another type of change produced in the brain and cord by toxoplasmosis is a non-suppurative leptomeningitis and disseminated encephalomyelitis, manifested by diffuse granulomatous changes, vascular proliferation and gliosis. Such changes were found in the C.N.S. of a 1-year-old labrador dog. This animal developed a partial paralysis of the hind-limbs; five weeks later it developed a complete posterior paralysis and after another week it became paralysed in the fore-limbs also.

The lesions present in spontaneous and experimental cases of toxoplasmosis in the dog vary considerably in distribution and in degree. However, in general, those most commonly described

have been pneumonia and miliary necrotic foci in the liver, ulceration of the stomach and small intestines, and necrosis of lymph nodes. Myocarditis with calcification has been described by Grocott (1950) and by others. Where necrosis has been extremely marked, several authors have likened the lesions to those produced by tuberculosis in the dog. It has been shown that although macroscopic lesions may be absent, all tissues, with the possible exception of bone, cartilage and areolar tissue, may show histopathological changes and may contain either free forms or pseudocysts.

### Sources of Infection

A possible reservoir of infection common to the human and the dog is to be found in rodents and perhaps the pigeon.

(1) *Rats.*—Perrin *et al.* (1943) showed 9% and Eyles (1952) 3% of wild rats in U.S.A. carried latent infections.

(2) *Mice.*—Spontaneous infections have been described in laboratory stock, but no surveys have been made on wild mice.

(3) *Rabbits.*—Acute and chronic infections have been reported in experimental rabbits, but no observations have been made on wild rabbits (Wiktor, 1950).

(4) *Wild hares.*—Clinical infections have been described in Denmark (Hulphers *et al.*, 1947; Christiansen and Siim, 1951).

(5) *Voles.*—Epidemic infections have been recorded in wild voles in Great Britain (Findlay and Middleton, 1934; Elton *et al.*, 1935).

(6) *Pigeons.*—Epidemics have occurred in laboratory stock (Wiktor, 1950). 5 to 9% of wild pigeons in Washington, U.S.A., were found to carry chronic infections of the mammalian form of toxoplasmosis (Jacobs *et al.*, 1952).

### Route of Infection

The usual route of infection in the dog is unknown, although some authors claim that the massive invasion of the intestinal mucous membrane seen in some cases points to an alimentary infection. Oral infection could possibly result from ingestion of infected rodents, or from contamination of food by excreta from infected rodents. Experimental evidence is now available that congenital infections may be produced in the dog and that infected bitches may excrete organisms in their milk (Chamberlain *et al.*, 1952).

Attempts to transmit toxoplasmosis experimentally via biting arthropods have failed, although it has been shown that arthropods which have fed on infected animals may harbour virulent organisms for a short while and may excrete them in the fæces. Infections could therefore possibly arise from ingesting infected ectoparasites or their excreta (Laven and Westphal, 1950; Blanc *et al.*, 1950; Piekarski, 1949; Weyer, 1951).

*Serological incidence.*—Table II gives a summary of surveys made on dogs by German workers: Otten *et al.* (1950); Otten (1952); Schmidt-Hoensdorf and Holz (1952). They appear to have found

Table II.—Serologically Positive Dogs (%)

| | | | |
|---|---|---|---|
| "Ill" .. .. .. | 72% | (118/164) | C.F. test |
| | 36% | (30/84) | Dye test |
| Encephalitis .. | 50% | (13/26) | Dye test |
| Chronic diarrhœa .. | 50% | (7/15) | Dye test |
| Healthy .. .. | 2–5% | (?/64) | Dye test |
| | 2% | (1/50) | Dye test |

a significantly high proportion of serologically positive cases among sick dogs. However, as few of these cases have been confirmed by the demonstration of the organism, it remains to be shown that this serological incidence gives a true picture of the incidence of clinical toxoplasmosis in the dog. Muhlpfordt (1951) has shown that sarcosporidia infections can produce positive titres to the Sabin Dye Test, and it is possible that other such non-specific reactions may occur.

*Evidence of transmission from dog to man.*—Table III shows percentage of serologically positive humans in contact with serologically positive dogs (Otten *et al.*, 1950). The values given for the

Table III.—Serologically Positive Humans (%)

| | | |
|---|---|---|
| In contact with: | | |
| Serologically +ve dogs | 60% | (23/38) |
| Serologically +ve dogs c enteric symptoms | 84% | |
| Serologically +ve dogs c nervous symptoms | 15% | |

Normal population 2–70%

proportion of the normal population possessing the cytoplasm modifying (dye test) antibody vary so greatly from place to place, and these results were based on so few observations that it is difficult to assess their significance. Fankhauser (1952) claims that a serological examination of families owning infected dogs gave no more positive reactions than did a population chosen at random.

Apart from a limited amount of serological evidence, little is known of the frequency of chronic inapparent infections in the dog. From analogy with the human and with other species studied experimentally it seems probable that such infections occur in the dog more frequently than clinically obvious acute cases. However, while it is reasonable to assume that an acute clinical infection, particularly one in which enteric symptoms predominate, represents a potent hazard to the human, the importance of latent infections of the dog in this respect is not yet known. Studies on chronic infections in other laboratory species would indicate that transmission to susceptible animals by contact alone does not occur.

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**Dr. J. C. Valentine** (Department of Pathology, Bedford General Hospital) demonstrated material from a case of congenital toxoplasmosis from which the parasite had been transmitted to laboratory animals. It is believed that this is the first time that animal inoculation from a human case has been successful in Great Britain.

The case was of a stillborn female infant born prematurely of a mother aged 31 with 2 healthy children aged 5 and 2 years. An insect bite and severe abdominal colic were the only abnormal features in the pregnancy. There were mice and possibly rats in the house in which she lived. She had contact with two cats and had prepared previously skinned rabbits for food.

Autopsy in the infant showed marked ascites with liver and splenic enlargement and slight jaundice. The cerebral hemispheres had been entirely replaced by yellow fluid and the containing membranes showed numerous yellowish plaques over their surfaces. The brain-stem, cerebellum and upper cervical cord showed areas of yellowish necrosis and hæmorrhage. There were opacities in the lenses of both eyes and hæmorrhage into the vitreous chamber. Microscopically the brain-stem showed a chronic inflammatory exudate with microglial nodules. In such areas numerous toxoplasmas were found in both the free and intracellular forms. Collections of 20–30 parasites were not uncommon but pseudocysts were not seen. The eye showed chronic inflammation of the disc but no parasites were seen.

Material from the brain-stem was inoculated by Dr. W. F. Lane into mice using the intracerebral route. The mice fell ill in about ten days with roughening of the coat and photophobia. Passage of the brains of these animals to further mice had similar effects. Numerous further passages were successful both in Dr. Lane's laboratory and also by Professor C. P. Beattie to whom one of the animals was sent. Both the intraperitoneal and intracerebral routes were used. The parasites became more numerous and the survival time shorter with repeated passage. After the eighth passage death occurred seven days after intracerebral inoculation. The brains of infected animals showed changes similar to those

seen in the infant, intracellular and free forms being found. Pseudocysts with silver-positive capsules could also be seen. Chorio-allantoic membrane was also successfully inoculated and the small white nodules found contained numerous toxoplasmas in the free form.

Serum from the family was examined by Dr. J. K. A. Beverley using the dye test and complement-fixation test. The results are given in Table I.

TABLE I

| | Dye test | Complement-fixation test |
|---|---|---|
| Mrs. F. | | |
| 6.1.53 .. .. | Positive 1/7,000 | Positive 1/32 |
| 11.2.53 .. .. | Positive 1/2,000 | Positive 1/80 (partial 1/160) |
| Mr. F. | | |
| 11.2.53 .. .. | Positive 1/14 | Negative |
| J. F., aged 5 | | |
| 11.2.53 .. .. | Negative | Negative |
| P. F., aged 2 | | |
| 11.2.53 .. .. | Negative | Negative |

Success in transmitting the disease to animals was probably due to the large numbers of parasites present in the brain of the infant. Had it not been born prematurely it is possible that the maternal antibodies would have destroyed the parasites and this probably accounts for the failure to transmit the disease in other cases.

**Mr. R. S. F. Campbell:** During the past few years much attention has been given to canine virus infection and encephalopathy at the Veterinary School at Glasgow University. The interpretation of some previous work was rendered difficult because of the conflicting opinions expressed by the authors. It would appear that when considering the various histological changes in the central nervous system the investigators had not related the lesions to the duration of illness of the cases which they studied. The assessment of some work was also hampered by the failure of the authors to demonstrate inclusion bodies due, probably, to the employment of unsuitable staining methods. In my experience, any combination of hæmatoxylin and eosin is inadequate for the consistent and vivid staining of the cytoplasmic inclusions of distemper. All staining methods are capricious to some extent. Like Dr. Trevan we have used the picro-Mallory stain with good results but our preference is for a modification of Lendrum's phloxin-tartrazine technique (Lendrum, 1947) which provides better differentiation. The intranuclear "inclusions" found in the astrocytes and other cells of the body in distemper present a problem for the histopathologist. Their significance is uncertain as it would be most unusual to find inclusions in one disease that differ somewhat in morphology and staining reaction as well as in their intracellular site. The nuclear bodies seen in distemper are Feulgen-negative, while the specific intranuclear inclusions of canine contagious hepatitis are Feulgen-positive. One wonders what significance may lie in that fact with relation to the viruses themselves.

The cribriform picture demonstrated in the cerebellar white matter by Dr. Trevan appears to be due mainly to acute oligodendroglial swelling. It should be remembered that, in a discussion of demyelinating diseases, Lumsden (1951) emphasized the probable relationship between these cells and the metabolism of myelin.

The gross appearance of the brain in Mr. Parry's type III suggests cerebral infarction which may have represented the effects of ischæmia produced by heavy perivascular cuffing in a late stage of distemper infection.

With regard to toxoplasmosis, a hint of the incidence of the disease in dogs is provided by the discovery of toxoplasmas in three out of a series of about 60 dogs with distemper-type infection studied by us at the Glasgow Veterinary School.[1] In 2 of the cases, the organisms produced a slight, focal encephalitic disease concurrent with the changes induced by the virus. The third dog showed toxoplasmas in a bronchial lymph node exhibiting extensive necrosis as well as the characteristic changes of distemper. An association between canine distemper and toxoplasmosis has been described by other observers in the past. It may be that acute generalized infection can stimulate the extension and development of a previously latent protozoal disease.

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[1] Since this meeting 1, and possibly 2, other cases of combined distemper and toxoplasmosis have been identified. The protozoal infection was generalized in both animals.

# Section of Neurology

President—MACDONALD CRITCHLEY, M.D., F.R.C.P.

[*May* 7, 1953]

MEETING HELD AT MAIDA VALE HOSPITAL FOR NERVOUS DISEASES, LONDON

**Palatal Myoclonus.**—H. LOVELL HOFFMAN, M.D., F.R.C.P.

Male, aged 58.

A coloured cine film of this patient was shown, demonstrating rhythmic myoclonus of the palate and muscles of the left side of the neck at 120 per minute.

*History.*—July 18, 1950: Sudden onset of left hemiparesis. B.P. 220/130. He was fully investigated at University College Hospital where a dorsolumbar sympathectomy was carried out in two stages on 22.11.50 and 11.12.50. B.P. fell to 140/90.

March 1951: B.P. 210/110.

August 1951: Right upper monoplegia.

May 1952: Started sea voyage to Vancouver; on reaching Azores, giddiness, headache and dysphasia, as a result of another cerebrovascular incident.

May 28, 1952: Admitted to Gorgas Hospital, Canal Zone, Panama. Left facial weakness, weak left arm and leg, spontaneous nystagmus. B.P. 230/144. Treated with potassium thiocyanate. B.P. fell to 154/122. Returned to England by sea.

August 1, 1952: Readmitted to University College Hospital. Right hemiparesis and expressive dysphasia, emotionally unstable.

December 17, 1952: Admitted to Nursing Home in Bath with acute retention of urine due to stricture, probably from catheter infection. Complaining bitterly of constant giddiness.

*On examination.*—In addition to the myoclonus described above there was Stage III retinal arteriosclerosis, ocular nystagmus to the left, lower right facial weakness. Palate moved to left on phonation. Weak flexion of right elbow, poor co-ordination and astereognosis of left arm. Weakness and poor co-ordination of left leg with increased tone. Tendon reflexes equal and brisk. Plantars, right extensor, left flexor. B.P. 220/160. The stricture was successfully dilated but the patient returned home and died in his sleep on February 10, 1953.

*Comment.*—It was suggested that the lesion was situated somewhere in the triangle, olive—dentate nucleus—red nucleus.

**An Unusual Case of Subacute Combined Degeneration of the Spinal Cord.**—SIR RUSSELL BRAIN, D.M., P.R.C.P.

D. M., aged 33.

*Complaints.*—(1) Weakness and sensory impairment in both legs for six months. (2) General listlessness for five years.

*History.*—At the age of 16 he lost the vision in the left eye fairly rapidly. Diagnosis of keratitis was made. Blood W.R. was positive. Treated with arsenic and bismuth for many years.

1942: Joined the Army. W.R. was negative.

For three years he has been liable to glossitis and ulcerative stomatitis.

October 1952: Whilst driving his car, he found he was making mistakes, putting his foot on the wrong pedal, since he was unsure where they were. He observed some awkwardness in walking, more marked in the right leg. Three months later, on getting out of bed, he found himself unable to walk at all since his legs were so weak and ataxic. In a few days this improved, so that he was able to get about with difficulty, but this has gradually deteriorated and he has remained in bed since February 1953.

Since January 1953, he has noticed a sensation of constriction around the abdomen at about the level of the umbilicus and he has also observed blunting of sensation to touch and temperature from the umbilicus downwards. At no time has he had "pins and needles", sensations in the limbs, disturbance of micturition or potency.

*On examination.*—Mental state. Normal.

*Cranial nerves:* I. Normal. II. VAR. 6/5. J.i. VAL. Hand movements only. Corneal opacity. Right visual field full; fundus normal. Remaining cranial nerves normal.

*Motor system:* Tone increased in the lower limbs.

*Power:* Symmetrical impairment in hip flexion, dorsi and plantar flexion of the ankles.

*Sensation:* Upper limbs—superficial and deep modalities normally appreciated. Lower limbs and trunk—sensation to touch, pin-prick, temperature, present in all areas but impaired on the right from T.12 to L.5 and on the left from T.10 to L.2. Sacral segments normal.

*Vibration sense:* Gross loss at toes and ankles.

*Reflexes:* BJ. + +
BRJ. + +
SJ. + +

Abd. $\frac{+ \quad +-}{+ \quad +-}$

KJ. ++ ++
AJ. ++ ++
P.Rs. ↓ ↓

*General examination.*—No abnormal physical signs. Blood pressure 125/70.

*Investigations.*—Blood: W.R. negative. Hb 84%; R.B.C. 3,770,000; W.B.C. 4,000. C.S.F. 70 mg. protein%. Lange 0111000000. W.R. negative.

Test meal: Histamine-fast achlorhydria.

Sternal marrow: Marrow of normal cellularity but a decrease in the myeloid-erythroid ratio and a marked megaloblastic transformation.

**Sensory Ataxia with Athetoid Movements.**—REDVERS IRONSIDE, F.R.C.P.

Miss C., aged 54. Five years ago she developed "pins and needles" and spastic weakness in the left leg with the sensation of a tight band below the left knee: nine months later paræsthesiæ in both hands, on the left side involving the two ulnar fingers, and on the right side the thumb, index and middle fingers. Her hands have become gradually more clumsy, especially the right, and her balance has become affected. The condition has not deteriorated in the last three years. The upper limbs are much more affected than the lower limbs.

There is slight right enophthalmos, the right pupil being smaller than the left; both pupils react normally. Marked athetoid movements occur in both hands, particularly the right, visible on purposive movements, worse if she is emotionally disturbed. The right hand sways wildly when extended with the eyes closed. The left hand sways slightly. There is gross sensory ataxia in the right upper limb, slighter in the left. Both lower limbs are slightly spastic, but not ataxic.

Sensitivity to cotton-wool is impaired on the right side from C.2 to T.9, and on the left side from T.2 to T.10. Light touch is absent over the left forearm and the ulnar border of the left hand. Pin-prick is diminished over the right arm up to the shoulder, and in the left arm up to the elbow. Temperature sensitivity shows impairment to hot and cold stimuli in both hands and over the ulnar aspect of both forearms. Vibration absent over the right radial styloid, the left fourth and fifth fingers, and over both tibial malleoli. Joint sense is absent in the fingers of the right hand and the left fourth and fifth fingers; it is normal in the toes.

The lower limbs show some indefinite blunting to pin-prick and cotton-wool from the ankles to the groins, especially on the left side.

All the tendon reflexes are absent; both plantar responses are extensor. The abdominal reflexes are absent upper and lower.

C.S.F. Cells 4 per c.mm. Protein 30 mg.%. Globulin, no excess. Lange 0000000000. W.R. negative. Blood count normal. X-ray of cervical spine, skull, and chest normal. Bronchoscopy, nothing abnormal seen.

Two sisters and one brother quite robust. No family history of any similar complaint.

**Dr. Ironside** said it was doubtful if the sensory changes alone could account for the athetoid movements. They had been observed when the patient's hand was at rest, and they were forceful.